International Council
on Alcohol, Drugs and Traffic Safety
(ICADTS)

Prescribing and Dispensing Guidelines for Medicinal Drugs Affecting Driving Performance

The ICADTS Working Group on
Prescribing and Dispensing Guidelines for Medicinal Drugs affecting Driving Performance

J.F. Alvarez (Co-chairman)
J.J. de Gier (Co-chairman)
A.S. Christophersen
M.C. Del Rio
A.C. Donelson
M.Z. Karlovsek
V.A. Maes
J. Mørland
Ch. Mercier-Guyon
E.J.D. Ogden
J.F. O'Hanlon
A.G. Verstraete
J.M. Walsh

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ICADTS is an independent nonprofit body whose goal is to reduce mortality and morbidity brought about by misuse of alcohol and drugs (licit and illicit) by operators of vehicles in all modes of transportation. To accomplish this goal, the Council sponsors international and regional conferences to collect, disseminate and share essential information among professionals in the fields of law, medicine, public health, economics, law enforcement, public information and education, human factors and public policy. The Council also publishes the proceedings of its conferences, reports of its working groups and a quarterly newsletter.

For information about **ICADTS** visit the website at: www.icadts.org, or contact President Barry Sweedler at Email: sweedlb@home.com, Tel: (+1) 925-962-1810 or Secretary Dr. Elisabeth Wells-Parker at Email: icadts@ssrc.msstate.edu, Tel: (+1) 601-325-7959.

For a copy of this report, contact Dr. Johan J. de Gier at Email: degiercs@wxs.nl, Tel: (+31) 162 456 900/Fax:(+31) 162 452 960.

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1. BACKGROUND

At T97, the 14th International Conference on Alcohol, Drugs and Traffic Safety in Annecy, France the Chairman of the Road Safety Committee of the Parliament of Victoria (Australia) challenged delegates in his address to the closing ceremony with a clear message: "*Research has not been able to establish confidently for other drugs (than alcohol) the point at which a particular drug makes a driver unsafe on the road. Scientists disagree on what driving-related tasks are important to road safety or even how experiments should be conducted. No internationally agreed testing procedures exist for measuring the effects of drugs on driver performance*". In its report the Victorian Road Safety Committee recommended the development of international scientific guidelines (Parliament of Victoria, 1996). The speech called on experts in drugs and driving to step forward and use their knowledge to establish guide-lines that would underpin effective legislation and prevention.

The International Council on Alcohol, Drugs and Traffic Safety (ICADTS) Executive Board took up this challenge and decided to create a forum within the membership for where these problems could be examined and debated. The first step was the establishment of an ICADTS Working Group on *Standardisation of Impairment Levels for Licit and Illicit Drugs in Transportation*. That Working Group was later subdivided. One group was set up on illegal drugs and a second on prescribed medications. The report of the first group, *Illegal Drugs and Driving*, has been published by ICADTS (Walsh et al., 2000).

The first working group considered that management of drug issues in transportation was similar to the management of drug problems in the workplace as discussed in the report "*Management of Alcohol- and Drug-related Issues in the Workplace*" (ILO, Geneva, 1996). Aspects of the drug problem of relevance to the drugs and driving problem include: social issues, public education, identification and testing, intervention, and the linkage between alcohol and drug problems. The experience of dealing with these issues in the workplace should be more generally applicable and therefore benefit the discussion in respect to transportation.

However, the management of drug related issues in the transport system should not be limited to the regulation of impairment. Preventive approaches are known to effectively diminish or deter drug use by drivers. Early interventions, such as improving prescribing and dispensing medication for patients who drive, had the potential to be a more efficient approach to traffic safety than attempts to regulate active compounds in body fluids. An additional ICADTS Working Group was established to consider *Prescribing and Dispensing Guidelines for Medicinal Drugs Affecting Psychomotor Performance.* The members of this group have worked to prepare the current report to serve as an invitation to (inter)national organizations of physicians, pharmacists, drug manufacturers and patients to formulate joint statements on the need to develop criteria for better warning systems, guidelines for safe application of psychotropic drugs and systems for disseminating information on impairing properties of medi-cinal drugs.

2. OBJECTIVES

The primary objective of this report is to provide guidelines for safe prescribing and dispensing of medicinal drugs to patients who operate motor vehicles, or other transportation vehicles[1].

By developing recommendations for improving warning systems and effective dissemination of these guidelines the Working Group members have started an international debate aimed at making patients and their health care professionals more aware of their responsibilities in relation to transportation safety. The approach to medicines and safety must be shared between the health professionals and patients. The Working Group members believe that a multi-disciplinary approach is needed if prescribing guidelines are to be well accepted by the community.

The sharing of responsibility between patients and professionals implies the involvement of more actors than simply the prescribers and dispensers.

- The pharmaceutical industry and the drug regulatory authorities must be included. Their involvement is needed to improve warning statements for medicinal drugs affecting driving performance. If the warnings are to be meaningful they should be based on specific research conducted according to methodological guidelines accepted by the international scientific community (Vermeeren, et al. 1993; De Gier, 1998; Berghaus et al. 1999).
- Health educators play an essential role in raising awareness of traffic safety issues among those who eventually will guide patients who drive to adopt responsible behaviours pertaining to traffic safety. Obviously teachers in medical and pharmacy schools, driving instructors and those who educate law enforcement officers all need to be involved.
- Above all patients have a "right to know" about risks they may take when combining medication and driving. As users of potentially impairing medication they must be educated to demand better warning systems so that they can take appropriate safety precautions before operating their vehicles.

The Working Group hopes that this document will encourage the international acceptance of prescribing and dispensing guidelines by professional organizations and regulatory agencies. By informing their various memberships and starting discussions about the guidelines provided in this document, they will play a key role in solving problems related to the use of medicinal drugs by patients who want to receive treatments safe for driving.

[1] The term "driving" as used in this report is meant to refer to the operation of any transportation vehicle, not just motor vehicles and the term "motor vehicle" shall include all transportation vehicles.

3. SUMMARY

In the introduction of this report the Working Group describes how in general physicians update their knowledge about behavioural effects of medicinal drugs on driving performance. Most of the sources they use are not conclusive in explaining whether or not a particular patient will become an unsafe driver after using a specific psychotropic medication. The Working Group provides several recommendations how to improve the application of existing knowledge by using a graded level warning system (Chapter 5). Obviously the information to be disseminated should vary according to the target population (the patient-driver, physician, pharmacist, authorities with responsibilities in road safety and public health). Several key-messages to these respective subgroups are given (Chapter 6). The prescribing and dispensing guidelines allowing physicians and pharmacists to prescribe and dispense the least impairing medicinal drugs for drivers are presented in Chapter 7. Special attention has been given to include prescribing and dispensing information that will allow patients to be more aware of recognizing signs of impaired driving performance if drugs with little or no impairment cannot be used to treat their disorders. Chapter 8 describes the problem of ensuring that information concerning driving impairing properties of medicinal drugs is effectively communicated to physicians, pharmacists and patients. Several information 'tools', such as warning systems, package inserts, categorization of medicinal drugs and guidelines for good medical and pharmaceutical practice have been discussed along with the means of implementation (education, regulation, media, information and communication technologies). Conclusions and recommendations are summarized and presented in Chapter 9.

The Working Group assessed the available scientific knowledge regarding guidelines for the regulation of medicinal drugs and the operating of motor vehicles. As a result of this assessment, the following recommendations are made:

Regulatory authorities should

- **Implement warning systems that are effective and made clear in package inserts of medicinal drugs, all in accordance with present knowledge of the drug's effects on ability to drive.**

- **Discuss with health professionals, patients and drug manufacturers how a three-tier categorization system could be used as a practical reference in addition to present statements in package inserts, in order to improve warning systems for patients.**

- **Discuss new procedures for assigning label and insert warnings for medicinal drugs in order to develop a framework for drug manufacturers, physicians and pharmacists that will encourage them to apply a three-tier categorization system that identifies each drug's potential for affecting patient's driving ability.**

- **Improve the structure of guidelines to assist drug manufacturers in applying methodologies of drug testing that will allow categorization of drugs and reconsider the use of standardized information for the warning section in package inserts and drug information leaflets.**

- **Establish an independent international centre for maintaining a three-tier categorization system for drugs based on consensus among experts in the field of drugs and driving.**

Professional (national and international) organizations of physicians and pharmacists should

- **Discuss and propose joint efforts for improving their prescribing and dispensing practices concerning drugs with impairing potential for patients who drive or operate machines.**

- **Encourage their memberships to prescribe and dispense the least impairing or safe drug within each**

class as an alternative for more impairing ones.

- **Discuss the key-messages to be disseminated in order to improve knowledge and to change attitudes of their membership in respect to medication and transportation safety.**

- **Utilize information and communication technology (ICT) for encouraging the use of guidelines on prescribing and dispensing mediation and for documenting consultations with patients about their experiences with the driving impairing properties of the drug. The development of databases and software to support these activities should be encouraged.**

Authorities with responsibilities in transportation safety and public health should

- **Present recent evaluations on the quality of present warning systems (unique meaning, simple or complicated, readability, interpretation by the end-user, etc) and its effects on patients who drive.**

- **Review the present knowledge in their respective countries regarding the relative risks of injury-accidents by users of different types of psychotropic medication and facilitate the application of drug use and transportation accident data bases for extending their knowledge and further targeting their countermeasures.**

- **Discuss the development of new regulations with respect to medicinal drugs and driving with patient/consumer, and driver organizations in order to determine what new regulations should be applied in daily practice addressing the public and the individual patient who drives.**

- **Encourage physicians and pharmacists to implement prescribing and dispensing guidelines.**

- **Develop media campaigns to address relevant issues that will focus on changing roles of patients, drivers, health care professionals, police officers, educators and driving school instructors.**

Organizations and research institutes in the field of drugs and driving should

- **Disseminate information on the safe use of medicinal drugs by drivers via the internet, addressing both the public and professionals. Provide quality assurance for the users of this source of information.**

Driving licensing authorities should

- **Meet their obligation for assuring applicant's fitness to drive when issuing or renewing driving licences. Develop effective lines of communication with medical and pharmaceutical practitioners to acquire information on the driving fitness and medication history of applicants.**

Medical and pharmacy schools should

- **Develop their educational programs pertaining to drugs and driving and to update these, if needed, based on present knowledge for safe prescribing and dispensing.**

4. INTRODUCTION

In practice, physicians and pharmacists update their knowledge about the behavioural toxicity of medical drugs from three major sources:

i) Package inserts approved by the drug regulatory authorities provide some information about known impairment of driving ability caused by the relevant substances;

ii) Articles in scientific journals and drug bulletins which discuss impairment of psychomotor performance of healthy subjects and/or patients under various test conditions attributed to various substances or groups of substances;

iii) Product specific mailings by the pharmaceutical industry claiming that their products are safe for drivers, or giving general warnings.

Some jurisdictions have programs to study the prevalence of licit drugs in the general driving population and in (fatally) injured drivers. This data can be used to estimate the relative risk of involvement in traffic accidents attributable to certain drugs. However, in most countries such data is lacking or the available data does not allow reliable estimation of the impact of drugs due to methodological problems (De Gier, 1999). Even where epidemiological data exists, it describes population risk and not individual risk.

Physicians and pharmacists deal with individuals. They have to decide whether or not a particular patient will become an unsafe driver after using a specific psychotropic medication. Population studies are not easy to interpolate for the individual.

When clear statements are made about driving risk, the prescriber and dispenser may not know the scientific basis of this advice, and therefore cannot judge its validity for their patients. Although there is international consensus in the scientific community on the methodology that ought to be used in evaluating the risk of medication for driving, the regulatory authorities have not formally adopted any guidelines. Consequently there are no guidelines to ensure the pharmaceutical industry performs standardised research. Physicians and pharmacists erroneously assume that regulatory agencies 'know their jobs' and therefore reliable, standardised testing has been conducted.

A proposal to introduce a graded level warning system for medicinal drugs affecting driving performance was presented to the European Union in 1991. Such a system would allow prescribers to chose the least impairing medication within each therapeutic class of drugs (Wolschrijn et al., 1991). Although a framework has been proposed, no pan-European or national regulatory body is categorizing drugs on the basis of their hazard potential for driving (Alvarez and Del Rio, 1994; De Gier, 1998).

Consequently, many physicians find that the problem of drugs and driving remains such a complex one, and that no solution is evident. Clinicians know that medication can produce unpredictable effects on performance. Clinical experience teaches that drug side-effects vary from person to person and are compounded by polypharmacy and self-medication. Impairment is often worse when drugs are taken in combination with alcohol. The picture is further complicated by recognising that some medical conditions may themselves impair driving, if not treated properly with medication (e.g. epilepsy, allergic rhinitis, depression). The general principle is that it is usually best clinical practice to prescribe the least impairing member of a therapeutic class, where a suitable drug is available.

When physicians have doubts about the ability of a patient to drive safely when undergoing drug treatment, they need to advise the patient to avoid driving. The required counselling is time-consuming. The message that medication is necessary but makes driving hazardous is hard for the prescriber to give and the patient to hear. Proper explanation requires a clear understanding of the risks of accident involvement under different treatment conditions.

There are good examples of pharmacoepidemiology research, in which drug-use data in a given population is linked to accident data in the same population to estimate relative risk. These studies show that patients exposed to

various types of psychotropic medication, such as benzodiazepines, are at increased risk (Herings, 1994; Hemmelgarn et al., 1997: Neutel, 1998; Barbone et al., 1998). Table 1 presents data showing the overall risk of some particular benzodiazepines and one cyclopyrollone hypnotic used in therapeutic doses and comparable blood alcohol concentrations.

Table 1. Relative risks of injurious road traffic accidents associated with the use of particular hypnotic and anxiolytic drugs and comparable blood alcohol concentrations (from Borkenstein et al., 1974).

Drug	Relative Risk	Comparable to BAC (%)	Reference
Diazepam	3.1	0.075	Neutel, 1998
Flurazepam	5.1	0.095	Neutel, 1998
Lorazepam	2.4	0.070	Neutel, 1998
Oxazepam	1.0	0.050	Neutel, 1998
Triazolam	3.2	0.075	Neutel, 1998
Zopiclone	4.0	0.080	Barbone et al.,1998

The risk is highest during the first two weeks of treatment. Extremely high relative risks have been reported with certain benzodiazepines: for example a 5 to 6 fold increase in accident risk, which is comparable to a blood alcohol concentration of 0.1% (Neutel, 1995). This implies that patients who commence treatment with a benzodiazepine must be advised that they should not drive in the first two weeks of treatment. If physicians do not give this advise, their patients have an increased risk of being involved in accidents, but do not know that they are taking the risk. Patients have a right to receive adequate information to enable them to decide whether or not to drive.

The following chapters will provide information needed by those who have to be involved in improving the decision making process by drug prescribers, dispensers and users.

5. A GRADED LEVEL WARNING SYSTEM

The European Union (EU) has formally defined criteria that allow categorization of drugs according to their impairing properties. The EU's Committee for Proprietary Medicinal Products (CPMP) Operational Working Party stipulated in its Note for Guidance for the Summary of Product Characteristics (III/9163/90-EN, Final approval 16 October 1991) that all medicines registered after 1 January 1992 can be categorized within the 'Warning' section of package inserts with respect to 'Effects on ability to drive or operate machines'. Article 4.7 in the original Note for Guidance states the following:

On the basis of

- *the pharmacodynamic profile, reported ADR's (adverse drug reactions) and/or*
- *impairment of drug performance or performance related to driving,*
  the medicine is:
  1. *presumed to be safe or unlikely to produce an effect;*
  2. *likely to produce minor or moderate adverse effects;*
  3. *likely to produce severe effects or presumed to be potentially dangerous.*

For situations 2 and 3, special precautions for use/warnings relevant to the categorization should be mentioned.

The original Note for Guidance (III/9163/90-EN) has been included in the rules governing medicinal products in the EU (Note for Applicants, Volume 2A, Procedures for marketing authorization, July 1997). In the latest version the reference "relevant to the categorization" in the last sentence has been omitted and the numerals "1, 2 and 3" for the categories have been replaced by "a, b and c".

Although every national regulatory authority usually follows EU guidelines closely, the categorisation has not been implemented according to a recent survey (De Gier, 1998).

International scientists proposed this three-tier categorization as the most feasible approach for the most frequently used psychotropic drugs (Wolschrijn et al., 1991). Information on this categorization and suggested drug lists was published in 1997 by the German Pharmacists Association (ABDA) and sent out to all German pharmacists (ABDA, 1997).

In Belgium, new legislation for detecting and prosecuting illicit drug use by drivers was accompanied by a campaign to inform the public and health care professionals about problems arising from the use of medicinal drugs by drivers (Grenez et al, 1999). The reason for addressing this issue is obvious: the proportion of European drivers taking medicinal drugs that could impair driving is 5 to 10 times higher than the proportion taking illicit drugs (De Gier, 1995). The Belgian campaign produced two leaflets, one for physicians and pharmacists explaining the various drugs in each of the different categories and one for patients summarizing this information. Unfortunately the list of drugs within categories has not been regularly updated.

International concerted action is required to extend the categories of drugs and make the lists more specific for the effects of different doses of the same drug and duration of action (e.g. for hypnotics). It is the Working Group's belief that new initiatives are needed, first by approaching drug regulatory and health care authorities in Europe, the USA and Australia for funding an international documentation and information centre responsible for maintaining the drug categorization system.

The following recommendations should be considered by drug regulatory and health care authorities for implementing a graded level warning system:

5.1 Discuss with health professionals, patients and drug manufacturers how a three-tier categorization system could be used as a practical reference in addition to present statements in package inserts, in order to improve warning systems for patients.

5.2 Discuss new procedures for assigning label and insert warnings for medicinal drugs in order to develop a framework for drug manufacturers, physicians and phar-macists that will encourage them to apply a three-tier categorization system that

identifies each drug's potential for affecting patient's driving ability.

5.3 Improve the structure of guidelines to assist drug manufacturers in applying methodologies of drug testing that will allow categorization of drugs and reconsider the use of standardized information for the warning section in package inserts and drug information leaflets.

5.4 Establish an independent international centre for maintaining a three-tier categorization system for drugs based on consensus among experts in the field of drugs and driving.

6. DISSEMINATION OF INFORMATION REGARDING MEDICINAL DRUGS AND DRIVING PERFORMANCE / FITNESS.

Research efforts in drugs and driving over the last two decades have not resulted in the provision of adequate information to the key-players, such as the driver-patient, prescribing physician and dispensing pharmacist. There is a lag time of many years before standard medical and pharmaceutical practice has adopted new treatment guidelines. Therefore authorities with responsibilities in the field of health care and transportation safety should make every effort to disseminate new information regarding medicinal drugs and driving performance as it becomes available. This chapter will be dedicated to the question *what* information needs to be disseminated. The question *how* this information should be disseminated will be discussed in the following chapters.

One of the key-messages on *what* information needs to be disseminated is the application of the three-tier categorization system. In order to make physicians, pharmacists and patients aware of the meaning of each category a comparison to the impairing effects of alcohol, which are well known, is suggested. Data collected in experimental research, in which over-the-road driving tests have been applied with most frequently used medicinal drugs and alcohol (as "calibration"), have allowed researchers to interpret weaving effects by any drug as equivalent to that produced by a particular blood alcohol concentration (BAC) (Louwerens et al., 1987). It will be easier to understand the severity of impairment by medicinal drugs if this concept could be communicated as follows:

Category	**Impairment description for medicinal drugs**	**Comparison with Blood Alcohol Concentration (BAC)**
I	Presumed to be safe or unlikely to produce an effect	Equivalent to BAC < 0.2 g/l (< 0.02%)
II	Likely to produce minor or moderate adverse effects	Equivalent to BAC 0.2- 0.5 g/l (0.02-0.05%)
III	Likely to produce severe or presumed to be potentially dangerous	Equivalent to BAC > 0.5 g/l (>0.05%)

Obviously, the information to be disseminated should vary according to the target population. The following target groups are suggested:

i) The patient-driver,
ii) Physicians and pharmacists,
iii) Authorities with responsibility in the field of road safety and public health.

The key-messages to these respective subgroups are the following:

- To the patient-driver:
  i) Recognise that some medicinal drugs impair driving performance / fitness more than others, and this has not been disclosed in package inserts.
  ii) Ask for further information from health care professionals about how to detect a possible impairing effect and what to do about signs of impairment.
  iii) Avoid the increased risk of medicinal drug effect on driving performance in case of the use of more than one drug, the use of over-the-counter drugs, and the use of alcohol along with the drug by following instructions given by the physician and the pharmacist.

- To the physicians and pharmacists:
  i) Know the medicinal drugs that can impair driving performance/fitness, according to their categorization.
  ii) Know how to select the least impairing medicinal drugs within each therapeutic class and apply the lowest possible dose.

iii) Inform the patient properly concerning the potential hazardous effects of the prescribed medication on driving performance, and provide them with clear instructions such as an advice not to drive at the start (two weeks) of some treatments (for example a benzodiazepine treatment).

- To the authorities with responsibility in the field of transportation safety and public health:
  i) Inform and convince the public and healthcare professionals that driving under the influence of certain medicinal drugs poses a risk to transportation safety.
  ii) Facilitate new research efforts, such as case-controlled pharmacoepidemiological surveys based upon existing data bases to determine the relative risk of traffic accidents for users of all drugs identified as potentially hazardous and disseminate the outcomes.
  iii) Review the initiatives that have been undertaken in other countries to reduce driving under the influence of medicinal drugs and apply the results of these initiatives if possible.

The following recommendations should be considered for defining the information to be disseminated regarding medicinal drugs and driving performance:

6.1 National and international (professional) organizations of patients, physicians and pharmacists should discuss the key-messages to be disseminated in order to improve knowledge and to change attitudes of their membership in respect to medication and transportation safety.

6.2 Authorities with responsibilities in transportation safety and public health should review the present knowledge in their respective countries regarding the relative risks of injury-accidents by users of different types of psychotropic medication and facilitate the application of drug use and transportation accident data bases for extending their knowledge and further targeting their counter-measures.

7. GUIDELINES FOR PRESCRIBING PHYSICIANS AND DISPENSING PHARMACISTS

In medical care it is standard practice to apply protocols for diagnosing and treating various medical conditions. In cases where medication has been selected as the preferred treatment option, side effects of medication that could harm the patient or diminish the drug's action should be avoided. In pharmaceutical care it is becoming standard practice to follow up patients who have indicated drug related problems that cause treatment failure or harm to the patient (Cipolle et al., 1998; Van Mil, 2000). Special attention is normally given to patients receiving a drug for the first time. In cases in which pharmacists have built trusting relationships with patients it is feasible to extend their services to include a duty of care for safe use of medication. In many European countries, the USA and Australia such pharmaceutical care is being well received, not only by the pharmacists, but also by health care authorities. These authorities are aware that this valuable pharmaceutical knowledge has been under-utilised for many years.

Guidelines for prescribing and dispensing practice must ensure that patients will get the maximum benefit of this knowledge. Ideally, all advice given to patients will have the approval of the respective professional organizations of physicians and pharmacists. It makes sense to involve educators and trainers in this process, so that all graduates understand their responsibilities and the advice they should give. In addition present knowledge of drug categorization should be used to adjust the existing guidelines for all major complaints and illnesses for which psychotropic drugs are prescribed. In other words: if psychotropic medication is the selected treatment option, the guidelines must refer to the benefits of using the least impairing drug within that therapeutic class.

Patient education has to be a substantial part of the prescribing and dispensing guidelines. Patients need to be educated about how to detect any undesirable effects on psychomotor functioning at the start of treatment and at all follow-up visits if repeat medications are prescribed. The advice given should be presented orally and in writing for maximum effectiveness. In rational prescribing and dispensing the following key-messages can be defined as essential parts (general and drug specific) of the guidelines to be developed for some frequently used therapeutic drug classes (O'Hanlon, 1995; Taylor, 1995; Del Rio and Alvarez, 1995; Alvarez, 1997; De Gier, 1997):

Prescribing Guidelines	**Dispensing Guidelines**
1. Realize that the use of some psychoactive drugs has been associated with an increased risk of causing an injurious accident and that patients should receive this information.	1. Discuss with prescribing physicians what patient information (written and oral) should be provided at the first delivery of a particular impairing drug
2. Consider an alternative in the light of experimental research showing large differences between the effects on driving performance of various drugs within the same therapeutic class .	2. Inform the prescribing physician that alternative drugs exist in case a drug in class II or III has been prescribed, and inform the patient.
3. Start with the lowest doses of psychoactive medical drugs and whenever possible avoid multiple dosing over the day.	3. Advise the physician to prescribe the lowest effective dose of a particular psychoactive medicinal drug and to avoid multiple dosing over the day . Inform the patient.
4. Do not reflexively "double the dose" if patients fail to respond to psychoactive medication.	4. Advise the physician to try another drug if the patient reports a lack of efficacy after beginning of treatment and inform the patient. If higher doses are needed advise the patient to use the largest part before sleep.
5. Avoid prescribing different psychoactive drugs in combination.	5. Explain to the patient that poly-therapy with psychoactive drugs is always an experiment with the patient's safety and to avoid driving if treatment can not be adjusted.

Prescribing Guidelines	Dispensing Guidelines
6. Do not rely upon the manufacturers' advice for counselling patients about the effects of drug upon driving.	6. Explain to the patient why warnings provided by the manufacturer about their drug's effects on driving are vague, illogical and sometime misleading.
7. Advise patients concerning the ways they can minimize the risk of causing a traffic accident if it is impossible to avoid prescribing an obviously impairing drug or one with unknown impairing potential (see next Table).	7. Advise the patient the ways they can minimize the risk of causing a traffic accident if they have to use a drug with an impairing potential (see next Table).
8. Monitor the patient's driving experience with the drug.	8. Monitor the patient's driving experience with the drug (e.g. at the first refill) and report back to the physician or ask the patient to inform the physician.

The prescribing and dispensing guidelines need to include drug class-specific guidelines in which reference to the least impairing drugs within the class can be given, as well as risk factors, and additional prescribing and dispensing information. Although it is difficult to advise a safe drug in drug classes in which these are not really available (e.g. the hypnotics), safer alternatives for anxiolytics and antidepressants exist. For example selective serotonin reuptake inhibitors are safe with little or no impairment of driving performance, as shown in experimental and epidemiological studies (Ramaekers, 1998; Barbone et al., 1998). These drugs are also effective in the treatment of anxiety disorders (Ballenger, 1999). Another safer alternative in treating generalized anxiety disorders is venlafaxine, an antidepressant acting by selective serotonin and norepinephrine reuptake inhibition (O'Hanlon et al., 1998).

The information provided in the next table are examples of drug class specific guidelines.

Drug class	Drugs with little or no impairment	Risk factors	Prescribing information	Dispensing information
Hypnotics	> 10 h post dosing; taken at night: Temazepam 10 mg Lormetazepam 1 mg Zolpidem 10 mg	Combination with other psychoactive drugs Liver and/or renal dysfunction (elderly patients: half the normal dose)	Avoid prescribing for longer than 2-4 weeks	1. Avoid alcohol while taking this drug If drugs with little or no impairment can NOT be dispensed and/or at the beginning of treatment (also with least impairing one) focus on: 2. Recognize signs of impaired driving performance (stop for rest if any occur): • Blurred vision • Difficulty in concentrating or staying awake • Unusual surprise by ordinary traffic events • Not being able to remember how exactly you came at destination • Difficulty in holding steady course in traffic lane 3 Avoid taking longer than 2-4 weeks and more than one at night

Drug class	Drugs with little or no impairment	Risk factors	Prescribing information	Dispensing Information
Tranquillizers	Buspirone 10 mg b.d.s.	No specific risk factors known	Avoid combination with selective serotonin reuptake inhibitors (SSRIs) because of reduced therapeutic effect Consider combination for 1 week with oxazepam 10 mg t.d.s. if therapeutic response seems to be inadequate (forbid driving during the first week)	1. Avoid alcohol while taking this drug If drugs with little or no impairment can NOT be dispensed and/or at the beginning of treatment (also with least impairing one) focus on: 2. Recognize signs of impaired driving performance (stop for rest if any occur): • Blurred vision • Difficulty in concentrating or staying awake • Unusual surprise by ordinary traffic events • Not being able to remember how exactly you came at destination • Difficulty in holding steady course in traffic lane
	SSRI's are effective in more than 60% of patients with generalized anxiety disorders : Fluoxetine 20 mg OD Paroxetine 20 mg OD	No specific risk factors known	Avoid combined use of fluoxetine and nonselective MAOIs, tryptophan, selegiline, terfenadine (adverse drug interactions) Avoid combined use of paroxetine and nonselective MAOIs, (dex)fenfluramine and selegiline (adverse drug interactions)	
	Venlafaxine 75-150 mg q.d. (an SNRI effective in more than 80% of patients with generalized anxiety disorders)	No specific risk factors known	Avoid combined use of venlafaxine and nonselective MAOIs (adverse drug interactions)	

Drug class	Drugs with little or no impairment	Risk factors	Prescribing information	Dispensing Information
Anti-depressants	Fluoxetine 20 mg OD Moclobemide 200 mg b.d.s. Paroxetine 20 mg OD	No specific risk factors known	Avoid combined use of fluoxetine and nonselective MAOIs, tryptophan, selegiline, terfenadine (adverse drug interactions) Avoid combined use of moclobemide and dextromethorphan, (tricyclic) antidepressants, (pseudo)ephedrine (adverse drug interactions) Avoid combined use of paroxetine and nonselective MAOIs, (dex)fenfluramine and selegiline (adverse drug interactions)	1 Avoid alcohol while taking this drug. If drugs with little or no impairment can NOT be dispensed and/or at the beginning of treatment (also with least impairing one) focus on: 2 Recognize signs of impaired driving performance (stop for rest if any occur): • Blurred vision • Difficulty in concentrating or staying awake • Unusual surprise by ordinary traffic events • Not being able to remember how exactly you came at destination • Difficulty in holding steady course in traffic lane
	Venlafaxine 75-150 mg q.d. (an SNRI effective in more than 80% of patients with generalized anxiety disorders)	No specific risk factors known	Avoid combined use of venlafaxine and nonselective MAOIs (adverse drug interactions)	
Anti-histamines	Ebastine 20 mg OD Loratidine 10 mg OD Fexofenadine 60 mg b.d.s. or 120 mg/180 mg OD	Liver and/or renal dysfunction		1. Avoid alcohol while taking this drug If drugs with little or no impairment can NOT be dispensed and/or at the beginning of treatment (also with least impairing one) focus on: 2. Recognize signs of impaired driving performance (stop for rest if any occur): • Blurred vision • Difficulty in concentrating or staying awake • Unusual surprise by ordinary traffic events • Not being able to remember how exactly you came at destination • Difficulty in holding steady course in traffic lane

NOTE:
Driving licensing authorities in different countries will identify minimum standards of mental and physical fitness to drive with respect to the regular use of psychotropic agents by applicants for or holders of a driving

licence. Both physicians and licensing authorities need to be clear on the restrictions to be applied in the case of regular use of high therapeutic doses being prescribed when a patient holds a driving licence. In particular, drivers of heavy vehicles require specific medical examination according to some laws. The licensing authorities should know the actual drug use by the applicant before issuing or renewing driving licences and decide on possible adverse effect on driving based upon the quantity of the drug taken by the applicant. But, how do licensing authorities know when applicants are taking drugs that hamper their ability to drive? European directives call for knowledge that licensing authorities cannot have under the present system, where there is no direct communication with prescribing physicians .

The following recommendations should be considered for defining the guidelines for prescribing physicians and dispensing pharmacists:

7.1 National professional organizations of physicians and pharmacists should discuss and propose joint efforts for improving their prescribing and dispensing practices concerning drugs with impairing potential for patients who drive or operate machines.

7.2 Authorities with responsibilities in transportation safety and public health should encourage physicians and pharmacists to implement prescribing and dispensing guidelines.

7.3 Driving licensing authorities should meet their obligation for assuring applicant's fitness to drive in issuing or renewing driving licences. Develop effective lines of communication with medical and pharmaceutical practitioners to acquire information on the driving fitness and medication history of applicants.

8. IMPLEMENTATION STRATEGIES

The objective of this chapter is to describe the problem of ensuring that information concerning driving impairing properties of medicinal drugs is effectively communicated to physicians, pharmacists and patients.
For each topic we should ask ourselves "What has been published to show the impact of existing means of implementation?". Furthermore, it is important to mention what we don't know.

Information 'tools':
1. Warning systems
2. Package inserts
3. Categorization of medicinal drugs
4. Guidelines for good medical and pharmaceutical practice

Means of implementation:
1. Education
2. Regulation
3. Media
4. Information and Communication Technology (ICT)

Warning systems
The effect of warning systems, such as warning labels and pictograms affixed to drug packages, so far has not yet been shown to change attitudes of drivers. Only a few small scale studies are known in the Netherlands and Sweden, but these were carried out almost twenty years ago (Stout and de Gier, 1982). Present warning systems are dichotomous in nature and do not take into account

- the differences in impairing properties of different substances within one therapeutic class
- the dose of the psychotropic drug
- the time after administration (hypnotics)

Although information on these issues exists from experimental research, warning systems have not been changed to include this knowledge in the presentation of the system. Furthermore, as far as we know, prescribing physicians and dispensing pharmacists do not communicate the differences in impairing properties between members of a class of drugs to patients.

This question needs to be addressed by the responsible government bodies and professional organizations. They need to review the recent evaluations on the quality of the warning system (unique meaning, simple or complicated, readability, interpretation by the user, etc) and its effect on the patient who drives. The question should be addressed to:

- Health authorities responsible for market authorization of medicinal drugs, health care, and welfare.
- Pharmaceutical manufacturers
- Experts in patient education
- Politicians
- Consumer/patient organizations
- Professional organizations of physicians and pharmacists

Warning systems can be implemented if regulatory authorities decide to include the system as part of drug regulation. Media, education and ICT will be instrumental in the actual application of the warning system by physicians, pharmacists and patients who drive.

Package inserts
There is a legal requirement to provide package inserts with medicinal drugs written in lay language. However, there has been little evaluation of whether or not the information provided under the section "Effects on ability to drive", is clear and understandable. Information on what the patient has to do in order to decide whether he or she can drive is vague, illogical and sometimes misleading. It should be clear whether it is safe to drive or not and under what circumstances (e.g. in combination with alcohol and other drugs). There is little or no information on what a patient can do personally to detect serious impairing properties of the drug.

The need for implementation of more effective information related to driving should be stressed to the responsible organizations (see the list presented above under warning systems). The application of a warning system should be clear in the package insert and should be in accordance with descriptions of the drug's adverse side effects concerning impairment of the ability to drive.

Categorization system for medicinal drugs affecting driving performance
Experience in the Netherlands, Germany, Belgium and Spain indicates that a cate-

gorization system for medicinal drugs affecting driving performance can be used to sensitise healthcare professionals and the public. Although there is some debate about whether or not there is need for three or more categories, there is sufficient knowledge and expertise to develop more standardization in determining the categorization for each drug. The use of a categorization system as a practical method to interpret long lists of adverse effects and warnings in package inserts seems to be promising.

Data from experimental research shows that there are extremes at both ends: the least impairing and the most impairing drug within each therapeutic class. It makes no sense to wait till all available psychotropic drugs have been assigned to one specific category. The use of the least impairing or safe drug within each class as an alternative to the more impairing ones needs to be promoted among physicians and pharmacists. This is a first step of implementing the categorization system and should have great impact in reducing drug related accidents.

Guidelines

The medical guidelines for prescribing must not only focus on prescribing the least impairing drug but also on increasing knowledge about the actual experience patients have with the prescribed medication. This is of particular interest in the case of renal or liver dysfunction where combinations of drugs are known to cause adverse reactions due to drug-drug interactions and where there is increased susceptibility for specific side effects especially with alcohol. This is of importance both for professional drivers and private drivers. The support of dispensing pharmacists in providing pharmaceutical advice should be studied further in order to provide guidelines for the further development of integrated care in which the information flows are standardised and shared among the different health care providers involved in caring for the patient.

Recognising that the first two weeks of benzodiazepine use are associated with collision risks higher than blood alcohol concentrations greater than 1.0 g/l (0.1%), a physician should prohibit a patient from driving for two weeks after starting the benzodiazepine (or any other psychotropic drug) and ask for feedback before prescribing a refill . At all times patients should be advised not to drive the first 2-4 hours after drug intake. It should be stressed to national and international professional organizations of physicians and pharmacists that benzodiazepines currently are the most widely prescribed psychotropic drugs and therefore of particular relevance with respect to increasing accident risks of patients who drive. Professional support in constructing new guidelines is paramount.

Special attention should also be directed to patients who are multi-drug users, whether for therapeutic purposes or who combine prescribed medication with illicit drugs. Guidelines should allow physicians to prohibit patients from driving while using a combination of drugs known to impair driving.

Education

The Working Group believes that physicians and pharmacists have a responsibility to know all about drugs and driving Professional education about drugs and driving is not recognized as a special topic in most countries . Medical and pharmacy schools should be asked to develop specific educational programs covering the risks of drugs and driving Research is also required to determine whether education of driving instructors, police officers and teachers in primary and secondary schools deals with this topic adequately. A starting point would be to develop five relevant questions that all health care professionals, police officer or driving instructors should consider when discussing drug impairment with patients, drivers, or applicants for a driving licence.

Most traffic laws prohibit driving licenses from being issued or renewed for applicants or drivers who are dependent on or regularly abuse psychotropic substances. This can be made clear to drivers or applicants, as a specific reason to avoid drug dependence.

Regulation

It is obvious that national regulations should provide better warning systems, and package inserts based on a categorization system for drugs impairing driving performance. If the regulations were stronger, guidelines for

health care professionals and educational programs on how to apply this knowledge will follow naturally. Collaboration between regulators and professionals should be encouraged to facilitate the development of guidelines and educational programs. There has to be partnership instead of an attitude of 'wait and see what will happen'. Health authorities should provide drug information bulletins free of charge to all health care professionals to update their knowledge.

Special attention should be given to patients who use high doses of psychotropic drugs and/or multiple drug users. European directives (Second Council Directive 91/439/EEC, Annex III, Art. 15.1) state 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". The Working Group believes that standard medical practice should be in accordance with this regulation.

Acceptance of any new or proposed regulation by the public is important. Therefore, it is of paramount importance to involve patient and consumer organizations in discussing the development of new regulations and how they should be applied in daily practice.

Media

The specific impact of media campaigns concerning drugs and driving is generally not known. However, changes in regulations and professional activities in relation to patients who drive needs to be disseminated so that thoughtful individuals can alter their behaviour. Media campaigns will support this if they are clear and well constructed to address the relevant issues. The impact will be greater if health care professionals, police officers, educators and driving school instructors have accepted their changing roles. Changing the behaviour of patients and drivers requires the dissemination of good information and education before decisions are made about drug treatment and/or driving while taking medication. Therefore, timing and coordination of activities will be crucial in achieving safety objectives.

Information and Communication Technology (ICT)

There are two important developments in Information Technology that will facilitate dissemination of information on drugs and driving. First the Internet provides many sources of information for the public and professionals. The standard of the information is very variable. The major organizations involved in traffic safety, drugs and driving should be asked to to provide quality assurance so that the users know which sources are reliable.

The second development is the application of ICT in the practice of prescribing or dispensing. The implementation of guidelines, the documentation of consultations with patients about their experiences with the driving impairing properties of the drug and the communication of feedback to the prescriber are facilitated by computerization in daily practice. The development of quality databases and software to support these should be encouraged.

The following recommendations should be considered for defining strategies to increase awareness and implement knowledge concerning driving impairing properties of medicinal drugs:

8.1 Responsible governmental bodies and organizations in transportation and public health should present recent evaluations on the quality of present warning systems (unique meaning, simple or complicated, readability, interpretation by the end-user, etc) and its effects on patients who drive.

8.2 Regulatory authorities should implement warning systems that are effective and made clear in package inserts of medicinal drugs, all in accordance with present knowledge of the drug's effects on ability to drive.

8.3 **Professional organizations of physicians and pharmacists should encourage their memberships to prescribe ands dispense the least impairing or safe drug within each class as an alternative for more impairing ones.**

8.4 **Medical and pharmacy schools should develop their educational programs pertaining to drugs and driving and to update these, if needed, based on present knowledge for safe prescribing and dispensing.**

8.5 **The development of new regulations with respect to medicinal drugs and driving should be discussed with patient/consumer, and driver organizations in order to determine what new regulations should be applied in daily practice addressing the public and the individual patient who drives.**

8.6 **Media campaigns should be clear and well constructed to address relevant issues that will focus on changing roles of patients, drivers, health care professionals, police officers, educators and driving school instructors.**

8.7 **Organizations in the field of drugs and driving should disseminate information on the safe use of medicinal drugs by drivers via the internet, addressing both the public and professionals. Provide quality assurance for the users of this source of information.**

8.8 **Professional organizations of physicians and pharmacists should utilize information and communication technology (ICT) for encouraging the use of guidelines on prescribing and dispensing medications and for documenting consultations with patients about their experiences with the driving impairing properties of the drug. The development of databases and software to support these activities should be encouraged.**

9. CONCLUSIONS AND RECOMMENDATIONS

A challenge was issued to the International Council on Alcohol, Drugs and Traffic Safety at the 14th International ICADTS Conference in Annecy, France (1997), to recommend international guidelines to assist in the regulation of medicinal drugs and driving. A Working Group was formed to consider the scientific basis for recommendations.

The Working Group concludes that the major problem is the lack of clear statements made about driving risk after taking psychotropic medication. This is surprising since there is now a vast body of evidence based on results from experimental and epidemiological research that shows that clear statements are feasible. Some drugs within a therapeutic class are considered as incompatible with driving (likely to produce severe adverse effects or presumed to be potentially dangerous), whereas others have minor effects or are presumed to be safe. These messages have not reached the prescribing physicians and dispensing pharmacists to an extent that they have improved their practices. Regulatory bodies should play a more defining role in changing this situation. The Working Group members conclude that a multidisciplinary approach is needed if prescribing and dispensing guidelines are to be well accepted by the community.

The sharing of responsibility between patients and professionals implies the involvement of more actors than simply the prescribers and dispensers.

- The pharmaceutical industry and the drug regulatory authorities must be included. Their involvement is needed to improve warning statements for medicinal drugs affecting driving performance. If the warnings are to be meaningful they should be based on specific research conducted according to methodological guidelines accepted by the international scientific community.
- Health educators play an essential role in raising awareness of traffic safety issues among those who eventually will guide patients who drive to adopt responsible behaviours pertaining to traffic safety. Obviously teachers in medical and pharmacy schools, driving instructors and those who educate law enforcement officers all need to be involved.
- Above all patients have a "right to know" about risks they may take when combining medication and driving. As users of potentially impairing medication they must be educated to demand better warning systems so that they can take appropriate safety precautions before operating their vehicles.

The Working Group members believe that an international debate aimed at making patients and their health care professionals more aware of their responsibilities in relation to transportation safety is just a first step. The proposed guidelines in this report are a second step and show how scientific knowledge can be applied for establishing practical guidelines to improve medical and pharmaceutical care. It is concluded that more collaboration between authorities in transportation safety and public health pertaining to the drugs and driving issues will eventually lead to more acceptance of these practice guidelines by the community. The Working Group therefore recommends that

Regulatory authorities should

9.1 Implement warning systems that are effective and made clear in package inserts of medicinal drugs, all in accordance with present knowledge of the drug's effects on ability to drive.

9.2 Discuss with health professionals, patients and drug manufacturers how a three-tier categorization system could be used as a practical reference in addition to present statements in package inserts, in order to improve warning systems for patients.

9.3 Discuss new procedures for assigning label and insert warnings for medicinal drugs in order to develop a framework for drug manufacturers, physicians and pharmacists

that will encourage them to apply a three-tier categorization system that identifies each drug's potential for affecting patient's driving abi-lity.

9.4 Improve the structure of guidelines to assist drug manufacturers in applying methodologies of drug testing that will allow categorization of drugs and reconsider the use of standardized information for the warning section in package inserts and drug information leaflets.

9.5 Establish an independent international centre for maintaining a three-tier categorization system for drugs based on consensus among experts in the field of drugs and driving.

Professional (national and international) organizations of physicians and pharmacists should

9.6 Discuss and propose joint efforts for improving their prescribing and dispensing practices concerning drugs with impairing potential for patients who drive or operate machines.

9.7 Encourage their memberships to prescribe and dispense the least impairing or safe drug within each class as an alternative for more impairing ones.

9.8 Discuss the key-messages to be disseminated in order to improve knowledge and to change attitudes of their membership in respect to medication and transportation safety.

9.9 Utilize information and communication technology (ICT) for encouraging the use of guidelines on prescribing and dispensing medication and for documenting consultations with patients about their experiences with the driving impairing properties of the drug. The development of databases and software to support these activities should be encouraged.

Authorities with responsibilities in transportation safety and public health should

9.10 Present recent evaluations on the quality of present warning systems (unique meaning, simple or complicated, readability, interpretation by the end-user, etc) and its effects on patients who drive.

9.11 Review the present knowledge in their respective countries regarding the relative risks of injury-accidents by users of different types of psychotropic medication and facilitate the application of drug use and transportation accident data bases for extending their knowledge and further targeting their countermeasures.

9.12 Discuss the development of new regulations with respect to medicinal drugs and driving with patient/consumer, and driver organizations in order to determine what new regulations should be applied in daily practice addressing the public and the individual patient who drives.

9.13 Encourage physicians and pharmacists to implement prescribing and dispensing guidelines.

9.14 Develop media campaigns to address relevant issues that will focus on changing roles of patients, drivers, health care professionals, police officers, educators and driving school instructors.

Organizations and research institutes in the field of drugs and driving should

9.15 Disseminate information on the safe use of medicinal drugs by drivers via the internet, addressing both the public and professionals. Provide quality assurance for the users of this source of information.

Driving licensing authorities should

9.16 Meet their obligation for assuring applicant's fitness to drive when issuing or renewing driving licences. Develop effective lines of communcation with medical and pharmaeutical practitioners to acquire information on the driving fitness and medication history of applicants.

Medical and pharmacy schools should

9.17 Develop their educational programs pertaining to drugs and driving and to update these, if needed, based on present knowledge for safe prescribing and dispensing.

The Working group hopes that this document will encourage the international acceptance of prescribing and dispensing guidelines by professional organizations and regulatory agencies. By informing their memberships and starting discussions about the guidelines provided in this document, they can play a key role in solving problems related to the use of medicinal drugs by patients who want to receive treatments safe for driving.

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11. MEMBERS WORKING GROUP

Prof. J. F. Alvarez (Co-chairman)
Drugs and Alcohol Research Group
Department of Pharmacology and Therapeutics
Faculty of Medicine
University of Valladolid
SPAIN

Prof A.S. Christophersen
National Institute of Forensic Toxicology
Oslo
NORWAY

Dr M.C. Del Rio
Drugs and Alcohol Research Group
Department of Pharmacology and Therapeutics
Faculty of Medicine
University of Valladolid
SPAIN

Dr A.C. Donelson
Failure Analysis Associates, Inc.
Engineering and Scientific Services
Menlo Park, CA
USA

Dr J. J. de Gier (Co-chairman)
Department of Pharmacoepidemiology
and Pharmacotherapeutics
University of Utrecht
THE NETHERLANDS

Dr M.Z. Karlovsek
Institute for Forensic Medicine
Medical Faculty
Ljubljana
SLOVENIA

Dr V.A. Maes
University Hospital
Brussels
BELGIUM

Dr Ch. Mercier-Guyon
CERMT
Annecy
FRANCE

Prof J. Mørland
National Institute of Forensic Toxicology
Oslo
NORWAY

Prof. J.F. O'Hanlon
Tri-Counties Regional Center
Santa Barbara, CA
USA

Dr E.J.D. Ogden
Applied Neurosciences
Brain Sciences Institute
Swinburne University
AUSTRALIA

Dr A.G. Verstraete
University Hospital
Gent
BELGIUM

Dr J.M. Walsh
The Walsh Group
Bethesda, MD
USA