Drugs and driving: an international categorization system

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1. Introduction

Information concerning the increased potential for risk in reducing driving ability while using hazardous drugs should be communicated to patients. This is especially important in those countries where, according to legislation, it is a punishable offence to drive a motor vehicle when driving ability has been impaired by a medicine.

Both The Netherlands and the Nordic countries recognized the need for a package warning system to inform patients using driving impairing medications. The Dutch system has been in effect since 1973 and the Nordic system since 1981. Both systems are based on a list of drugs (generic substance names) that can affect driving.

According to a national agreement between the Dutch professional organizations of physicians and pharmacists, any pharmacist filling a prescription for a drug on the list, dispenses the drug with a yellow label bearing the warning (in black): "This medicine can influence your driving ability". As a result of pharmacy automation most pharmacists do not use these labels any longer. The warning now appears as an integral part of the dispensing label with dosing instructions for the patient.

In addition to label warnings issued by pharmacists, the Netherlands' registration authorities require special warnings for drivers in the package insert for all drugs possessing known side effects that are potentially hazardous. In general, pharmacological class warnings have been the rule. According to recent EC directives, patient package inserts in all EC member states should contain special precautions for use of impairing medicines relevant to a specific categorization of impairment severity after January 1st, 1994.

The system used in the Nordic countries is maintained by the Nordic Committee on Medicines. A label showing a red triangle is affixed to all packages of drugs within a category entitled 'especially dangerous'. At the request of the prescribing physician, the label may also be affixed to drugs within another category entitled 'potentially dangerous'. Pharmacists dispensing medications labeled in this way are required to provide the patient with a leaflet containing additional information.
Present systems have failed to meet their promise.

Systems using pharmacological class warnings and drug lists for package warning labeling were at the time of their creation based on little or no empirical data to support a drug categorization. The lack of information regarding the differential drug and dose effects resulted in a skeptical attitude of prescribing physicians. They had to wait and see whether the predicted impairment applied into the individual patient. Their drug prescribing activities could not be supported by guidelines for selecting a less impairing drug. A general warning to alert the patient or no information at all was the effect of the existing systems.

Several experts have argued for improvement within the present system of class warnings, because it does not allow for dose effect and impairing effect found some time after ingestion (e.g. in the case of hypnotics). This information, however, is available for many drugs and should be used for more rational prescribing of drugs to patients who can be expected to drive or operate machinery while taking medication. Developments in empirical research support a more graded level system and call for the implementation of a differential system. A system based on a proper categorization of many different medicinal drugs and doses of the same drugs, with respect to the severity of psychomotor impairment they produce.

2. New categorization system

Deficiencies within the existing categorization systems were recognized in The Netherlands by a Task Force, started in 1986 with an assessment of the various opinions of the parties involved. It had unofficial status and its membership included representatives of the major national traffic safety and drug regulatory agencies, along with others from professional associations of physicians and pharmacists, patient/consumer advocacy groups, the Netherlands Association of Pharmaceutical Manufacturers and scientific institutions engaged in drugs and driving research. The Task Force initiated a study to group driving impairing drugs within categories of severity. The Institute for Drugs, Safety and Behavior was commissioned in 1988 by the Ministry of Welfare, Health and Cultural Affairs, the Directorate of Public Health for drugs, the Ministry of Transport and Public Works, and the Netherlands' Royal Association for the advancement of Pharmacy (who also cooperated in the execution of the study) to design a new categorization system.

2.1 Study design

The study design was based on the premise that the categorization of drugs suspected of having driving impairing properties is possible using expert opinions obtained from questionnaires. A literature survey alone to categorize driving impairing drugs was not expected to be successful, since there is still much variability in the way studies of drug effects on driving performance are conducted.
2.1.1 Consultation of experts

After determining the opinions of some experts in the field of drugs and driving and policy making about a graded level categorization system, the final questionnaire was distributed among a group of 45 recognized experts in Europe, North America and Australia. The purpose of the expert rating questionnaire was to determine whether a consensus existed concerning the severity of drug effects. Furthermore, it was important to show whether experts engaged in research on psychoactive drugs were able to categorize the drugs they studied.

2.1.2 Design of the categorization system

The new categorization system had to be constructed in a way that data available from the literature and expert ratings could be translated into easily accessible information and that experts could agree on the categorization of drugs. In a pilot feasibility study a draft categorization system used for rating the antidepressants consisted of three categories, showing increasingly impairing effects on driving performance and one category to define a lack of information. As a result of this pilot study the design of the categorization system was extended somewhat.

2.1.3 Feedback round with the results of the expert ratings

The experts' opinions are based upon a complex integration of both published and unpublished observations, direct clinical experience or general knowledge, hearsay, and even unfounded biases. The degree of error contained in many experts' opinions would be expected to affect the degree of consensus they are able to achieve, when categorizing a particular drugs' effect on driving. However, unless that error is biased, the central tendency of opinions should be a valid estimate of the drugs' hazard potential. The central tendency would only be an invalid indicator if affected by a systematic bias arising from experts' misconception of the true drug effect. Therefore it was decided to consult the experts again in a feedback round and to present all experts' ratings in order to arrive at a final consensus.

3. Results

3.1 Expert opinions

For the final questionnaire 45 researchers were selected on the basis of the number of their publications on drugs and driving or drugs and psychomotor performance. The response rate (67%) and reasons for non-respondence are listed in Table 1.
Table 1. Response rate to the final questionnaire

<table>
<thead>
<tr>
<th>Response</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>personally N= 26</td>
<td>30</td>
<td>67</td>
</tr>
<tr>
<td>same as investigational partner N=4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reasons for non-response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>disagreement with the objectives or with the study design</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>not enough knowledge/no longer in this field of research</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>lack of time/to much work</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>unknown</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>101</td>
</tr>
</tbody>
</table>

The thirty respondents received an anonymous feedback of the response of colleagues to the final questionnaire. They were again asked to categorize drugs from the final questionnaire. The response to this feedback round was 93%.

3.2 Categorization

The proposed categorization system is given in Table 2. There was a need to divide the original category expressing moderate effects into two. This would allow the experts to state that the one II-class drug is not as impairing as the other II-class drugs, but is not devoid of detrimental effects. In addition to this, the category II* was added, to categorize those drugs suspected of only light psychotropic effects (e.g. some beta-blockers or H2-antagonists) or drugs for which enough experimental studies were available to conclude that no severe impairment would occur, but for which not enough is known to conclude whether they produce moderate, light or no impairment.
Table 2. The proposed categorization system.

<table>
<thead>
<tr>
<th>Category I</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Drugs unlikely to produce an effect on driving performance: In various experimental circumstances negligible or no impairment of driving performance or performance related to driving is repeatedly demonstrated.</td>
</tr>
<tr>
<td>I* Drugs presumed not to be dangerous based on their pharmacological profile, even though there are no experimental studies that support this presumption.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category II</th>
</tr>
</thead>
<tbody>
<tr>
<td>II&lt;sub&gt;1&lt;/sub&gt; Drugs that can produce minor adverse effects on driving performance: Some impairment of driving performance or performance related to driving is seen in some experimental circumstances.</td>
</tr>
<tr>
<td>II&lt;sub&gt;2&lt;/sub&gt; Drugs that can produce moderately adverse effects on driving performance: An impairment of driving performance or performance related to driving is seen in various experimental circumstances.</td>
</tr>
<tr>
<td>II* Drugs that will not produce severely adverse effects on driving performance: But because of a lack of sufficient experimental studies it can not be established if the effect is moderate, light or absent. (Should be treated as II-class drug).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category III</th>
</tr>
</thead>
<tbody>
<tr>
<td>III Drugs likely to produce severely adverse effects on driving performance: In various experimental circumstances gross impairment of driving performance or performance related to driving is repeatedly seen.</td>
</tr>
<tr>
<td>III* Drugs presumed to be potentially dangerous based upon their pharmacological profile: But there are not sufficient experimental studies to support this presumption (Should be treated like III-class drugs).</td>
</tr>
</tbody>
</table>

* = Theoretically derived category. Necessary for including those drugs which have not been sufficiently investigated.
3.3 Final response

The responses after the feedback round provided a categorization of a total of 573 drug doses in different formulations or effects after a certain time-interval following drug administration (like in the case of hypnotics). For 145 of these drug doses 6 or more experts responded.

3.4 International cooperation

In spite of time constraints, the size of the questionnaires and the fact that participation was voluntary, the majority of experts was prepared to cooperate. The experts cooperating in this study work in several countries, which resulted in an expert rating with an international character (Table 3).

<table>
<thead>
<tr>
<th>Country or group of countries</th>
<th>Number of ratings</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom</td>
<td>629</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>495</td>
</tr>
<tr>
<td>Finland/Sweden/Denmark</td>
<td>361</td>
</tr>
<tr>
<td>USA/Canada/Australia</td>
<td>243</td>
</tr>
<tr>
<td>Germany/Switzerland</td>
<td>229</td>
</tr>
</tbody>
</table>

3.5 Calculations

The expert ratings were summarized and translated into group scores by summing up the scale values (Table 4) and dividing the total by the number of ratings. To serve as an example: 5 experts rated diphenhydramine 50 mg as moderately impairing (value 3) while 3 rated it as severely impairing (value 4). The mean value resulting from these ratings is: \([5 \times 3] + (3 \times 4)\) : 8 = 3.4. Mean values were used for graphical expressions of drug doses (see Figures).
Table 4. Values assigned to the categories.

<table>
<thead>
<tr>
<th>Category</th>
<th>value</th>
<th>short description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1</td>
<td>no impairment</td>
</tr>
<tr>
<td>I*</td>
<td>1</td>
<td>no impairment</td>
</tr>
<tr>
<td>II_1</td>
<td>2</td>
<td>minor impairment</td>
</tr>
<tr>
<td>II_2</td>
<td>3</td>
<td>moderate impairment</td>
</tr>
<tr>
<td>II*</td>
<td>3</td>
<td>no severe impairment</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>severe impairment</td>
</tr>
<tr>
<td>III*</td>
<td>-</td>
<td>unknown effects, but suspected</td>
</tr>
<tr>
<td></td>
<td></td>
<td>of impairment</td>
</tr>
</tbody>
</table>

3.6 Interpretation of the data

There are no specific rules for determining consensus based on this type of rating. That is why the authors followed their own judgement and determined that a consensus existed whenever

* 6 or more experts responded within the same category and
* 85% or more of the experts agreed with the ratings as given by the others.

Category III* was not included as it expresses the fact that not enough information is available to make a reliable conclusion and consequently does not add information about the degree of impairment.

The following figures show examples of the average expert rating and corresponding impairment severity category for various drugs as a function of their respective minimum therapeutic doses. The degree of expert consensus regarding the place of the drug/dose within the indicated category is given by symbols:

• = 86%-100%  ● = 70%-85%  ■ = <70%
dotted line = 5 experts responding.

For hypnotics the expressions are given as a function of effect of time after administration.
Figure 1. Average expert rating and corresponding impairment severity category for various tranquillizers as a function of their respective minimum therapeutic doses.
**Tranquillizers**

**Figure 2.** Average expert rating and corresponding impairment severity category for various tranquilizers as a function of their respective minimum therapeutic doses.

SEC = secobarbital 50 mg
CLR = clorazepate 5 mg
CLD = chlordiazepoxide 5 mg
DIA = diazepam 2 mg
ALP = alprazolam 0.25 mg
CLB = clobazam 10 mg
Antihistamines

Average Rating (arb.units)

Dose (x minimum)

PRO = promethazine 25 mg
TRI = triprolidine 2.50 mg
TRI SR = triprolidine 'slow release' 10 mg
CLE = clemastine 1 mg
DPH = diphenhydramine 25 mg

MEQ = mequitazine 5 mg
CET = cetirizine 10 mg
TER = terfenadine 60 mg
LOR = loratadine 10 mg
AST = astemizole 10 mg

● = 86%-100%; ○ = 70%-85%
• = <70%; — — — = 5 experts

Figure 3. Average expert rating and corresponding impairment severity category for various antihistamines as a function of their respective minimum therapeutic doses.
Antidepressants

Figure 4. Average expert rating and corresponding impairment severity category for various antidepressants as a function of their respective minimum therapeutic doses.
Figure 5. Average expert rating and corresponding impairment severity category for various hypnotics as a function of effect of time after administration.

DIA = diazepam
OXA = oxazepam

= 86%-100%;  = 70%-85%;
= <70%;  = 5 experts
Hypnotics

Average Rating (arb.units)

8-12 h 12-16 h 16-22 h
time after administration (h)

FLU = flurazepam
TRZ = triazolam
ZOP = zopiclon

= 86%-100%; = 70%-85%;
= <70%; = 5 experts

Figure 6. Average expert rating and corresponding impairment severity category for various hypnotics as a function of effect of time after administration.
Figure 7. Average expert rating and corresponding impairment severity category for various hypnotics as a function of effect of time after administration.
Hypnotics

Figure 8. Average expert rating and corresponding impairment severity category for various hypnotics as a function of effect of time after administration.
4. Discussion

4.1 Establishment of criteria

Most respondents were able to provide information about drugs within one or two pharmacologic groups. A few experts were able to categorize drugs of several pharmacologic groups. This may increase the risk that the severity of effects is not judged equally for every group. The rank order within a group, however, will not change substantially as seen in the figures.

A remaining and most important issue is the establishment of criteria for determining to which category a drug will be assigned. A consensus meeting on guidelines for studies and study design among investigators in this field is needed for the establishment of these criteria. For example, by using 'calibration drugs' (drugs known to be more or less severely impairing in almost every study published on these drugs) in standardized doses that could serve as indicators for severity of impairment in every pharmacologic group, experts are able to give their views and opinions in a more standardized way. By using these 'calibration drugs' in well structured studies and study designs, future studies published in the literature will yield the possibility of comparison of conclusions on the impairing properties of every psychoactive drug.

The Institute for Drugs, Safety and Behavior started to investigate this view among experts as part of a questionnaire on methodological criteria for standardizing research on drugs affecting driving performance. This study is commissioned by the National Swedish Road Safety Office and The Netherlands' Ministry of Transport and Public Works. The first responses have been discussed during an International Workshop on Methodology in Man-Machine Interaction and Epidemiology Studies in Padova (Italy), October 28 to November 1, 1991. The final response will be discussed during T92 in Cologne.

4.2 Description of the proposed categorization system

The questionnaire used in our study comprised a comprehensive list of oral drugs with suspected effect on driving performance. Although the information was restricted to a categorization based upon the acute effects of drugs when given in a standard dose to healthy subjects, may differentiating factors need to be taken into account for the application of the categorization. Some of these factors can be described as important characteristics of the proposed system:

Severity of impairing effect: Unlike the present categorization systems, which are based on pharmacologic groups, the new system is based on the degree of behavioral impairing effect for every drug dose and drug formulation. This should enable physicians to choose the least impairing drug within a given pharmacologic group.
Car driving abilities: Although several complex psychomotor tasks are influenced by psychotropic drugs, car driving is used as one of the most hazardous activities in every-day life and can cause risk to others. Extrapolations to other psychomotor tasks should, however, be possible.

Dose and formulation: The system is based on the dimensions of dose and formulation (e.g. sustained release, soft gelatin capsules) as a strong dose/formulation effect is seen in some drugs. The present Dutch system categorizes by compound only.

Acute effects: Because the majority of empirical studies investigate acute effects (mainly for economical reasons), the categorization system is based on these acute effects on the premise that the rank ordering will not change with multiple dosing. Also, patients suffer most severely from impairing effects and must adjust to these in the acute phase of treatment.

Residual effects: The usual experimental procedure in the investigation of impairing effects of hypnotics is to measure residual effects that occur after sleeping. Consequently there is a need to define residual effects. For hypnotics the categorization system was extended to include three time intervals; 8-12 hours (morning), 12-16 hours (midday-afternoon) and more than 16 hours after administration.

Healthy young subjects: The system is based on the effects as measured in young healthy subjects. One reason from this is that the majority of studies is carried out on this group, but an other, more basic reason is that such a homogenous group is most likely to provide reproducible results with higher precision. It is arguable whether such a categorization system can adequately represent the reactions of patients treated with drugs over longer periods. However, it may be assumed that the rankordering will not differ for patients.

4.3 Need for concerted actions

One of the benefits of the categorization system is that it will improve standardization of a number of activities related to the problem of drugs and driving. Standardization of research methodology is a topic that is much emphasized in former reviews.

Standardizing future research: Information on the behavioral toxicity of new drugs is becoming an important issue. Using 'calibration drugs' for establishing the criteria of the different categories, future comparisons with new drugs in well designed studies should yield the information for categorization of drugs by expert panels.
Standardizing drug registration procedures: Drug manufacturers need criteria for standardized methods as at this moment it is problematic to provide registration authorities with sufficient proof of absence or degree of impairment. Concerted actions will be needed to investigate present registration procedures and to survey opinions of registration authorities who must decide upon the impairing properties of a compound.

Guidelines to indicate driving license restrictions: Traffic safety authorities might choose to regulate driving license restrictions for certain groups of road users at risk. By identifying the behaviorally toxic drugs according to the categorization system, the patient and/or his physician need further information on how to react responsibly. The procedures to be followed might have an impact on the patient's attitudes to report his medicine use. They will also affect the physicians reporting on the patients' ability to operate a vehicle. Concerted actions are needed to formulate practical guidelines and recommendations for this purpose.

Harmonizing patient warning systems: Recent EC-Directives state that both the 'Summary of product characteristics' provided to health care professionals, and 'Package inserts' for patient use, should contain a section providing information about possible psychomotor impairing effects of the drug concerned. International drug package warning systems need to be implemented based upon the categorization system presented in this paper. A concerted action will be needed to harmonize the required information given to patients.

Drug use evaluation: The involvement of pharmacists and physicians in computerized dispensing and prescribing offers the opportunity to design pharmacoepidemiologic studies, linking drug files of patients to data on hospital admissions and accident involvement. Concerted actions for determining relationships between the drivers' use of medication in different hazard categories and their respective risks of involvement in vehicular accidents, will influence policy makers, health care providers and patient/consumer advocacy groups in deciding on measures needed to minimize risks patients experience as a result of behaviorally toxic drug reactions.

Concerted actions as mentioned above need to be internationally oriented and would be major undertakings best accomplished by a supranational body such as the European Community (EC) drug regulatory authority or the World Health Organization (WHO).
5. Conclusion

In conclusion, this study has demonstrated the feasibility of a new categorization system for medicinal drugs affecting psychomotor performance, based upon expert consensus. Such a system would not be immediately comprehensive and might well serve only as an interim solution. Implementation should only follow after greater efforts than were employed in the present study, to ensure that experts are adequately informed and that possible common biases are eliminated. The success of the final implementation has to be the result of a series of concerted actions for harmonizing research methodologies, registration procedures, package warning systems and traffic safety regulations. The long-term outcome would be an improvement of both patient and public safety.

6. References