State of
Knowledge of
Drug-Impaired
Driving

FINAL REPORT

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16. Abstract Examines the current state of knowledge of drug-impaired driving. The review covers a broad range of related research, including the detection and measurement of drugs in drivers, experimental research on the effect of drugs on the performance driving-related tasks, drug prevalence in various populations of drivers, drug-crash risk, and countermeasures for drug-impaired driving. The review covers scientific literature published since 1980.			
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INTRODUCTION AND APPROACH

This is the final report of a project entitled "State of Knowledge of Drug-Impaired Driving." The project was conducted by Mid-America Research Institute, Inc., of New England for the National Highway Traffic Safety Administration (NHTSA). David Shinar of Ben Gurion University of the Negev, Israel, and J. Michael Walsh of The Walsh Group, Bethesda, Maryland, made significant contributions. This review examines research published during the 1981-2001 period and references some of the earlier material contained in prior reviews.

The scope of the review included foreign as well as U.S. literature with a direct bearing on highway safety. The review emphasizes *controlled substances* to include marijuana, benzodiazepines, non-benzodiazepine sedative and hypnotic drugs, and others such as amphetamines, cocaine, hallucinogens, and narcotic drugs. However, research related to any other drugs having the potential to significantly impair driving is also included in the review. Applicable research conducted in foreign countries, and documented in the English language, is included.

This report is presented in six substantive chapters. Chapter 2 contains a description of the methods followed in determining the topics and issues of concern in the review, identifying, acquiring and screening the documents to be reviewed, and reviewing individual documents. Chapter 3 deals with research pertinent to the detection and measurement of drugs in drivers, and Chapter 4 reviews the experimental literature, including research conducted in a laboratory testing human performance on tasks believed to be related to driving, and research conducted either in a driving simulator or on a closed course testing performance in actual driving tasks. In Chapter 5, we examine literature flowing from epidemiologic studies of drugs and traffic crashes, including literature on the drug use of various subgroups of drivers such as drivers arrested for drunk driving or "drugged" driving. Chapter 6 deals with literature on countermeasures for drug-impaired driving, and Chapter 7 presents our conclusions and recommendations. An index of terms and a bibliographic listing of references follow at the end of the report.

Our conclusions and recommendations are organized by the four major types of scientific literature examined in the review, namely:

- Detection and measurement of drugs in drivers,
- Experimental research on the effects of drugs on performance of driving-related tasks.

- Epidemiologic research on the drugs in driving populations, including drivers in crashes, on-the-road drivers not in crashes, and drivers suspected or convicted of drug-impaired driving.
- Research on countermeasures for drug-impaired driving.

The conclusions and recommendations are presented below. Examples of documents supporting the specific conclusions are cited, and cross references to pages of this report discussing more general conclusions are provided.

DETECTION AND MEASUREMENT OF DRUGS IN DRIVERS

Conclusions

- A variety of specimens can be assayed for drugs, including urine, blood, sweat, saliva, and hair, among others. Each specimen is unique, and each offers different patterns of information about drug use over time (page 11).
- Most laboratories use immunoassay screening technology with gas chromatography-mass spectrometry (GC/MS) confirmation. Over the last 20 years the cost of using these technologies have become affordable, and most laboratories now have the equipment, the assays, and the expertise to identify the most commonly used drugs (page 14).
- While there have been significant improvements in laboratory assays for drugs of abuse, the value of such improvements to highway safety specifically is limited by an insufficient number of laboratories incorporating these improvements.
- The reliance solely on the forensic laboratory to assay all specimens in all cases limits the number drug-impaired driving cases that can be prosecuted, because there are simply not enough forensic resources currently available.
- Point-of-contact-testing (POCT) devices offer promise for alleviating this problem. For example, these POCT devices could be used by police officers to routinely screen DUI suspects for illegal drug use and obtain drug test results immediately, as they currently do with alcohol tests (page 15).
- Until there is adequate capability for rapid, cost-effective drug testing, many drugged drivers will not be identified or prosecuted.

Recommendations

- Federal and state agencies concerned with traffic safety should provide additional support to enhance forensic capabilities to detect and measure drugs in drivers.

■ The forensic community should give more attention to the new POCT technology and work to integrate this technology with laboratory testing into a more efficient and cost-effective system for detecting and quantifying drugs other than alcohol in drivers.

EXPERIMENTAL RESEARCH

Selected literature on the effects of a wide range of drugs on performance of driving-related tasks and performance of actual driving tasks was reviewed. Classes of drugs considered were:

- narcotics,
- central nervous system (CNS) depressants,
- CNS stimulants,
- cannabis,
- antidepressants,
- antihistamines, and
- other drugs that have been investigated in a few individual studies.

Conclusions

■ The amount of research in these classes varies widely, with the most attention given to CNS depressants and the least given to narcotics. We found essentially no experimental research on some other classes of drugs not listed above, for example, hallucinogens and inhalants.

■ With respect to the acute effects of drugs, it appears that the following drug classes have a high potential for significant impairment of driving and driving-related performance:
   ✓ narcotics (Stevenson, Pathria, Lamping, et al. (1986),
   ✓ long-life benzodiazepines in therapeutic doses (Soames, 1982),
   ✓ short-life benzodiazepines in high doses (Kunsman, Manno, Przekop et al., 1992),
   ✓ barbiturates (Mintzer, Guarino, Kirk, et al. (1997)),
   ✓ 1st generation H1 antihistamines (Moskowitz and Wilkinson, 2003; Starmer, 1985), and
   ✓ certain anti-depressants, that is, amitriptyline, doxepin, and mianserin (see page 44).

■ Drugs classes with a relatively low potential for significant impairment after acute usage are:
   ✓ CNS stimulants (which actually may improve performance at low doses in some instances) (Ward, Kelly, Foltin, and Fischman, 1997),
   ✓ 2nd generation H1 antihistamines (Starmer, 1985) , and most other anti-depressants (page 47).

- The literature suggests that acute use of cannabis has a moderate potential for impairment (Lamers and Ramaekers, 1999).
- Very few studies have examined the chronic and sub-chronic use of the above classes of drugs, and most of those that have suggest little effect on driving and driving-related performance.
- All-in-all, the literature supports the common-sense notion that drugs with a strong sedative action taken in the highest doses have the highest potential for significant impairment, while others have the lowest potential. Other meta-generalizations about which tasks and functions are impaired by which doses of which drugs cannot be made on the basis of the literature we examined.

Recommendations

- Current experimental research should be continued, with emphasis on newly emerging drugs with potential to impair driving performance.
- More research should be performed to determine the effect of chronic as well as acute use of drugs on the performance of realistic driving-related tasks. Such research should include both closed-course studies, and also simulator studies of the types possible in the National Advanced Driving Simulator at the University of Iowa.

EPIDEMIOLOGIC RESEARCH

Conclusions

- A significant amount of new information has been added to the pool of scientific knowledge about the role of several classes of drugs in traffic crashes since the last state of knowledge update. However, gaps still exist on certain drug classes that are in widespread use, for example, antihistamines and antidepressants.
- The literature suggests that the prevalence of the drugs that have been studied in driver populations, while not negligible, is much smaller than the prevalence of alcohol in such populations.
- The literature indicates that chemical tests of drivers in North American crashes were performed most often for narcotics, benzodiazepines, barbiturates, cocaine, amphetamines, and cannabis.
- Of these drugs, cannabis/marijuana has been found the most often by a wide margin. This should not be surprising, given the findings of the 2001 National Household Survey on Drug Abuse (U.S. Department of Health and Human Services, 2002) that 76% of current users of illicit drugs were users of this cannabis/marijuana.

- For fatally injured drivers, cannabis had the highest percentages testing positive, ranging from 7% to 37% with a mean of 14%. The mean percentages of each of the other five drugs amounted to about 5% or less (page 82).
- Few of the reviewed studies examined the percentages of various drug classes found in non-crash-involved drivers (page 81). Only two drugs were found to be present in more than 1% of the drivers: benzodiazepines (4% in a Canadian study and a mean of 3% in other foreign studies), and cannabis (5% in the Canadian study).
- Except for benzodiazepines, the percentages of drug-positive drivers suspected by the police of driving under the influence of drugs were about the same in foreign studies as in U.S. studies, ranging from an average of about 13% for barbiturates to 28% for cannabis (page 85). Benzodiazepines appeared in an average of 30% of suspected drivers tested in foreign studies versus 14% in the U.S. studies. Only one foreign study (in Switzerland) had data for cocaine use (11%), and the U.S. studies indicated an average of about 16% of the tested suspects were positive for cocaine.
- The role of drugs as a causal factor in traffic crashes involving drug-positive drivers is still not understood. Drug risk factors are still not known with acceptable precision, with some evidence suggesting little or no increase in crash risk at drug levels being detected by current chemical test procedures. Available evidence (page 83) suggests a maximum risk factor of about 2.0 occurring for benzodiazepines and cannabis, followed closely by narcotics at 1.5. CNS stimulants (including cocaine and amphetamines) were associated with either no increased risk factor (cocaine) or even a decreased risk factor (other stimulants).
- Current research does not enable one to predict with confidence whether a driver testing positive for a drug, even at some measured level of concentration, was actually impaired by that drug at the time of crash. This is in sharp contrast to alcohol where BAC measurements can provide a good estimate of impairment.

Recommendations

- With respect to drug prevalence, the state of knowledge about the prevalence of drugs in traffic crashes in the U.S. should be updated periodically. Drugs of interest should include those currently in vogue among user populations.
- With respect to drug-crash risk, a program of research should be undertaken to assess the traffic-crash risk associated with the potentially impairing drugs that current knowledge suggests are the most prevalent in serious traffic crashes in the United States. This research program should compare the drug use of drivers who were involved in crashes with that of a

similar group of drivers who were not involved in crashes. The program should concentrate first on fatal crashes and should be of sufficient geographic scope to enable some reasonable assessment of the general magnitude of any drugged-driving problem nationwide. Clearly, such a research program poses some formidable difficulties, especially with respect to drugs in on-the-road, non-crash involved drivers. Nevertheless, work must begin if further progress is to be made in defining the drug-crash problem in this country.

COUNTERMEASURES FOR DRUG-IMPAIRED DRIVING

Conclusions

- Countermeasure approaches in the United States and Europe have involved the use of the Criminal Justice System to enforce drugged driving laws using methods similar to those used in enforcing alcohol-impaired driving laws.
- The major emphasis in these countermeasures is the identification of impairment among stopped drivers using chemical tests and / or clinical assessments.
- We found no evaluations of the impact of any drugged driving countermeasure on crashes, either in the United States or Europe. This might be expected, given the lack of any databases containing objective measures of the presence of drugs in crash-involved drivers.

Recommendations

- Determine the effect on traffic crashes of existing drug-impaired driving countermeasure programs in selected jurisdictions.
- Develop ways of improving the response of the Criminal Justice System to drug-impaired driving, including legislation, enforcement, adjudication, and sanctioning.
- Identify new, more innovative approaches to dealing with drug-impaired driving with initial emphasis on drug classes known to have higher potential for creating drug-crash risk.
- Increase the extent and intensity of research and development efforts to apply technology to drug-impaired driving.
- Provide more funding support to the efforts of operational agencies involved in current drug-impaired driving countermeasure efforts.
- Establish an integrated, long-term drug-impaired driving program at the federal level incorporating the above elements in a phased approach.

1 - INTRODUCTION

This is the final report of a project entitled "State of Knowledge of Drug-Impaired Driving." The project was conducted by Mid-America Research Institute, Inc., of New England for the National Highway Traffic Safety Administration (NHTSA). David Shinar of Ben Gurion University of the Negev, Israel, and J. Michael Walsh of The Walsh Group, Bethesda, Maryland, made significant contributions, Professor Shinar writing much of the material in Chapter 4, and Dr. Walsh writing the bulk of Chapter 3. Dr. Walsh also reviewed the provisions of state laws on drugged driving contained in Chapter 6. This review of drug-impaired driving examines research published during the 1981-2001 period, and references some of the earlier material contained in prior reviews.

The first comprehensive review of the state of knowledge about drugs other than alcohol and highway safety in this country was the landmark report by Joscelyn and Maickel (1975). That review was updated in a report by Joscelyn, Donelson, Jones, et al. (1980) which provided input to NHTSA's 1979 report to Congress on drugs and driving (National Highway Traffic Safety Administration , 1979). About this same time, NHTSA had sponsored the study *Drug Research Methodology* which laid some of the groundwork for future research in this field (Donelson, Marks, Jones et al., 1980). The last update review of the state of knowledge about drugs and highway safety was conducted by Compton (1988) and was also documented in a report to Congress. In the meantime, there has been some significant research in the field, some of which has been sponsored by NHTSA, but much of which has been conducted outside the United States. This update review examines the validity and utility of research published since December 31, 1980 for developing public policy, including policy relating to the development of new research and development initiatives.

The remainder of the body of this report is presented in six chapters. Chapter 2 following this introduction contains a description of the methods we followed in determining the topics and issues of concern in the update; identifying, acquiring and screening the documents to be reviewed; and conducting the individual reviews. Chapter 3 is concerned with research pertinent to the detection and measurement of drugs in drivers, and Chapter 4 reviews the experimental literature, including research conducted in a laboratory testing human performance on tasks believed to be related to driving, and research conducted either in a driving simulator or on a closed course testing performance in actual driving tasks. In Chapter 5, we examine literature flowing from epidemiologic studies of drugs and traffic crashes, including literature on the drug use of various subgroups of drivers such as drivers arrested for drunk driving or "drugged" driving. Chapter 6 deals with literature on countermeasures for drug-impaired driving, and Chapter 7

presents our conclusions and recommendations. An index of terms and a bibliographic listing of references follow.

2 - METHOD

The materials reviewed here are those dealing with the drug-crash problem created by various groups of drivers. The scope of the review included foreign as well as U.S. literature with a direct bearing on highway safety. The review covers the period 1980 to the present and addresses the following four major areas of research:

- detection and measurement of drugs,
- experimental research,
- epidemiologic research, and
- countermeasures for dealing with drug-impaired driving.

The review emphasizes *controlled substances* to include marijuana, benzodiazepines, non-benzodiazepine sedative and hypnotic drugs, and others such as amphetamines, cocaine, hallucinogens, and narcotic drugs. However, research related to any other drugs having the potential to significantly impair driving is also included in the review. Applicable research conducted in foreign countries, and documented in the English language, is included.

Specific topical areas examined for literature are:

- Types of drugs that have been addressed in the scientific literature pertinent to traffic safety, and the general nature of their biokinetics, their measurement, and their acute and chronic effects on the human body.
- Effects of these types of drugs on behaviors related to driving-related performance and to driving performance.
- Drug usage and patterns of usage in the general driving age population.
- The presence of drugs in various types in crashes, that is:
  - ✓ Fatal crashes,
  - ✓ Non-fatal crashes,
  - ✓ Crashes involving pedestrians and bicyclists.
- The crash risk created by drug usage -- the question of causality.
- Characteristics of people who use drugs and drive, including:
  - ✓ Biographical variables – for example, age, sex, race, ethnicity, income;
  - ✓ Driving variables – for example, where, when, types of vehicles, traffic law violations, trips;
  - ✓ Drug usage variables – for example, where, when, frequency, problem users;
  - ✓ Other variables – for example, psychosocial factors, medical conditions.

■ Approaches to dealing with the drug-impaired driving problem, and the effectiveness of those approaches, for example:

:

✓ Legal,
✓ Health,
✓ Educational,
✓ Public Information and Education,
✓ Technological,
✓ Alternative transportation.

■ Methodologic problems in all of the above areas of research.
■ Future research needs in all of the above areas.

ISSUES

Major issues considered when reviewing a document were:

■ *Subjects and subject selection.* Whether the study's subjects were representative of the general population of drivers, were a special group selected perhaps as a matter of convenience, or were selected in some manner that makes it difficult to determine exactly who they were and what group they represented.
■ *Nature of the data used in the study.* Whether the data used in the study were valid for quantifying the study variables, that is, which kinds of specimens (blood, urine, other) were analyzed for which drugs; how were the specimens collected and preserved; how were they analyzed; and how were the results classified?
■ *Findings of the study.* Of major concern in this respect is whether the findings are consistent with the study design, the data acquired and used in the study, and the analysis of the data. Inappropriate interpretations of a study's results have to be explicitly identified, even though we did not necessarily discard an otherwise useful study because its findings were somehow flawed.
■ *Nature and appropriateness of the statistical techniques.* Whether the study contains a clear explanation of the statistical techniques, and whether the techniques described were appropriate for detecting practically meaningful differences between groups that were compared in the study.
■ *Drugs as a causal factor.* If a clinical approach was used, whether the procedure used led to a plausible conclusion as to whether drugs *could* have caused the crashes studied. If an experimental approach were used, issues of the comparability of the crash group and the comparison non-crash group will arise, along with issues related to the method used for determining any relative risk factors developed from such an analysis. Of

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major concern will be the issue of whether drug presence among drivers studied is being extrapolated inappropriately to mean causation.

SOURCES OF LITERATURE

Literature sources included collections and individual documents that have not been placed in traditional collections. Types of repositories that were contacted include:

- Specialized libraries of highway safety literature maintained by such organizations as NHTSA, The University of Michigan Transportation Research Institute (UMTRI), and the Insurance Institute for Highway Safety;
- Specialized computerized information services such as the Transportation Research Information System (TRIS) and its highway transportation subfile Highway Research Information System (HRIS), MEDLARS, MEDLINE, and EMBASE;
- Specialized information clearinghouses and abstracting services such as National Institute on Drug Abuse; Johns Hopkins University's Alcohol, Drugs, and Driving: Abstracts and Reviews; the Addiction Research Foundation (Canada); Alcohol, Drugs and Traffic Safety: Current Research Literature;
- General libraries having collections in related disciplines such as medicine, law, and the social sciences; and
- General repositories and information services maintained by governmental agencies such as the National Technical Information Service and the Library of Congress.

The UMTRI library was the central focus and coordinating element of the literature search and collection activities. The research library at Purdue University was also accessed in the literature search.

LITERATURE SEARCH PROCEDURES

The starting point in the search was recent bibliographies and reviews of directly related materials. Relevant bibliographies and reviews were identified through a search of the UMTRI library, and through discussions with subject-matter experts (including a project advisory group) and others.

The next step in the search was to examine specific journals and conference proceedings known by the principal investigators to contain pertinent materials. These documents were not necessarily concerned directly with highway safety, but tended to focus on other related disciplines such as human factors, toxicology, and drug studies in general.

Another source considered for this review is material generated by the various Drug Evaluation and Classification (DEC) programs throughout the country. This material appears in different forms, including newsletters and pseudo-journals that report claims on the accomplishments of the programs, some of which are supported by data. NHTSA staff in Washington identified a number of contacts for gaining access to such materials.

Each document acquired through the literature search was screened for inclusion in this review. Two levels of screening were performed: (1) an initial screening to determine whether a document should undergo further substantive examination by the Principal Investigator (Mr. Jones), and (2) a final screening by the Principal Investigator of documents surviving the initial screening. Criteria contained in each these levels are indicated below:

- Level 1 - Initial Screening
    - ✓ Criterion 1.1 - The document must address pertinent topics as it appeared to when it was identified initially.
    - ✓ Criterion 1.2 - The document must at least *purport* to have scientific validity. Documents merely reflecting the unsupported opinions of their author were not retained for review.

- Level 2 - Final Screening
    - ✓ Criterion 2.1 - The study documented must *actually have* scientific validity, that is:
        - ‣ The study's objectives and the hypotheses being examined must be clearly stated. The study design and the research method must be appropriate for accomplishing the study's objectives, and must be thoroughly described in the document. *It is essential that the characteristics of the study's subjects and how they were selected be described, and that the selection criteria were consistent with study objectives.*
        - ‣ The quality of the data must adhere to generally acceptable standards for scientific research.
        - ‣ Sample size (N), and the probability of a result occurring by chance alone (p) are reported.
        - ‣ The actual amount of differences among groups that may be compared in a study (that is, effect size), and the level of significance for rejecting the null hypothesis of no differences (α) are reported.
        - ‣ The analysis techniques used are appropriate and properly used.
    - ✓ Criterion 2.2 - The treatment of the results of the study must be complete, objective, and balanced, and the findings and conclusions must be sound.

Failure of a document to meet either of the Level-1 criteria resulted in its elimination from the review. However, documents that met Level-1 criteria but

were flawed with respect to one or more Level-2 criteria were not necessarily rejected. For example, a study that was well-designed and executed, but made conclusions that did not flow from its findings might have been kept in the update. The update's commentary on that study noted the inconsistencies between the research results and the conclusions, and offered a more consistent interpretation of the results. Some other flawed studies that were being widely quoted in the non-scientific literature were retained simply to document their flaws.

Finally, the last step in conducting the update was the preparation of this document, the update report. Bibliographic information on each article was entered into a computerized bibliographic database.

3 - DETECTION AND MEASUREMENT OF DRUGS

INTRODUCTION AND BACKGROUND

In comparison with the alcohol literature, relatively little information is available regarding the true incidence and prevalence of illegal drug use in reckless driving and impaired driving crashes. Breath-alcohol testing has established a scientifically sound basis for the estimation of the prevalence of alcohol use among reckless drivers (Dubowski, 1992). However, the principal problem with estimating "drugged" drivers has been the relative unavailability of drug detection methods / devices to routinely test for illegal drugs. In general, such testing capabilities have been limited to highly specialized forensic laboratories (Joscelyn, Donelson, Jones et al., 1980; Turk, McBay, and Hudson, 1974), and even there, have not used routinely.

Available epidemiological research examining drugs other than alcohol indicates that cannabis is by far the most prevalent drug detected in impaired drivers, fatally injured drivers, and motor vehicle crash victims (Marquet, Delpla, Kerguelen et al., 1998; Morland. J., 2000; Risser, Stichenwirth, Klupp et al., 1998; Verstraete and Puddu, 2000; Walsh, Buchan, and Leaverton, 1997)[1]. Other drugs occurring with relatively high frequency are benzodiazepines, cocaine, opiates and the amphetamines (e.g., MDMA, methamphetamine, and d-amphetamine sulfate). While many other drugs are found in injured or killed drivers, these five categories of drugs (i.e., cannabis, benzodiazepines, cocaine, opiates and amphetamines) appear to makeup the majority of the problem as currently understood. While new technology has made available new devices for drug detection, there appear to be a number of practical reasons why we do not have better data on the true prevalence of drugged driving:

- Police are generally not trained to look for drugs other than alcohol.
- Specimen collection requires special equipment and training
- Many state laws limit police to a single test, and the initial test is usually a breath test.
- Most state laws do not provide for additional penalties for combination of alcohol and drugs; therefore if the suspect exceeds the BAC limits there is no incentive to look for drugs.
- Crime labs often cannot provide results in a timely manner to meet court deadlines and to relate test results to time of drug-taking; thus, prosecutors

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[1] Epidemiologic literature on drugs other than alcohol is reviewed in Chapter 5.

must drop the drug charge, and as a consequence police lose interest in collecting specimens for drug testing.

In an earlier update of this subject, Joscelyn et al. (1980) provided an excellent summary of the state of the art in the detection and quantification of drugs in body fluids. This discussion included detailed descriptions of the general techniques including: thin-layer chromatography (TLC), gas chromatography (GC), gas chromatography-mass spectrometry (GC/MS), Immunoassay (IA), and high-pressure liquid chromatography (HPLC). Over the last 20 years of technological advances much has changed, but it is surprising how much lab practice has remained the same. In this update we will describe new methodological and technological innovations, and summarize some of the current thinking about detecting drugs in drivers.

A variety of specimens can be assayed for drugs, including urine, blood, sweat, saliva, and hair, among others. Each specimen is unique, and each offers different patterns of information about drug use over time. ? illustrates the general relationship between drug effects and the detection periods in various specimens. Each specimen has strengths and weaknesses about the level of information that can be gained about drug use. State laws generally stipulate which specimens may be tested for drugs for criminal justice applications. (See Chapter 6 for a discussion of criminal justice countermeasures.)

Figure 3-1: Drug Detection Periods In Various Specimens

From E. J. Cone, Addiction Research Center, NIDA
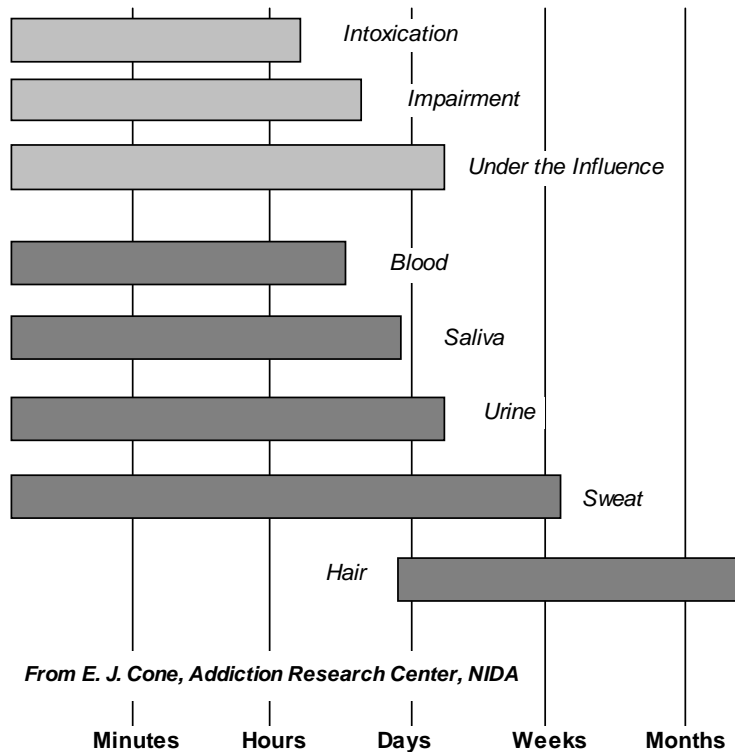
GENERAL METHODS AND SPECIMENS FOR DRUG SCREENING

Blood Testing

Due to the invasiveness of the collection procedure and the cost of laboratory analysis, routine screening of blood for drugs in drivers has generally been viewed as impractical. Augsburger (2002) recommends a three-step laboratory-analysis process for determining the effect of drugs on driving performance. However, in recent years, forensic laboratories have seen an increasing number of specimens for determination of drugs in blood as a result of "zero tolerance" laws and better trained police officers who have been trained to recognized drivers under the influence of drugs (Moeller and Kraemer, 2002). This is especially true in Europe where several European countries (e.g., Sweden, Germany, and Belgium) have enacted per se laws for driving under the influence of drugs. These laws stipulate urinalysis as the preliminary screening test, and require a blood test if the urine is positive for drugs. Under these laws, any level of prohibited drug detected in the blood is considered evidence of driving under the influence.

In terms of attempting to link drug concentrations to behavioral impairment, blood is probably the specimen of choice. However, forensic toxicologists generally have failed to agree on specific plasma concentrations that could be designated as evidence of impairment (Consensus Development Panel, No Date). The lack of consensus about per se levels of drugs where impairment could be deemed makes it difficult to identify, prosecute or convict drugged drivers in most states.

Oral Fluid (Saliva) Testing

Mixed saliva, which is the most accessible matrix used for the detection of drugs, consists primarily of secretions from the submaxillary (65%), parotid (23%) and sublingual (4%) glands (Kintz, 1999). Detection times for drugs in oral fluids are roughly similar to that in blood, approximately 1-24 hours. (See Kintz for an extensive discussion on detection times by drug.) Oral fluids normally contain the parent drug substance rather than drug metabolites such as are present in urine. Collection of oral fluid is generally considered less invasive than either blood or urine, and could be an excellent matrix to tie recent drug use with behavioral impairment.

Typically the analysis of oral fluids is conducted in a laboratory. There are a number of new rapid immunoassay tests and other analytic methods (e.g., ion scanning, up-converting phosphor technology) that have recently become available and may eventually be suitable for use at the roadside. The current problems with oral fluid testing whether done in the lab or potentially at the roadside include:

- Some drugs inhibit salivary secretions (e.g., MDMA) making collection difficult.
- There is no consensus on cutoff levels for confirmation of drugs in saliva.
- Oral fluid assays for most drugs of abuse are still in the developmental stage, and an accurate/reliable assay for cannabis (the most prevalent drug tested in drivers) is still illusive to diagnostic manufacturers.
- There are no nationally established standard methods for oral fluid drug testing, nor are there any certification programs currently available.

Recent evaluations of available rapid point-of-collection oral fluid tests with drivers indicate the specificity, sensitivity and positive predictive values for drugs of abuse have been poor (Verstraete and Puddu, 2000). Cannabinoids appear to be especially difficult to detect in oral fluids, as very little drug is excreted into the saliva. At this time, none of the currently marketed rapid devices appears to be able to accurately and reliably test for marijuana at cutoff levels that would be helpful in enforcing laws dealing with driving under the influence of drugs (DUID). A number of rapid point-of-collection saliva tests for alcohol are available and have been approved by the Food and Drug Administration (FDA). Some on-site alcohol devices have been included by NHTSA on their conforming products listing as suitable for use as screening test devices in the Department of Transportation (DOT) workplace testing programs (See the NHTSA internet site, www.nhtsa.dot.gov).

Sweat Testing

Drugs are excreted in the sweat mostly in the form of the parent compound. The collection of sweat over time can produce a cumulative record of prior drug use. According to Kintz (1999), since sweat is a cumulative medium, a positive result should not be regarded as "conclusive evidence of driving under the influence (much like urine), but rather as an indication of recent exposure." Sweat testing methods for drugs have recently been approved by the FDA, and include a sweat patch collection device. This patch is designed to collect drugs of abuse from human skin. The patch (from Pharmchem Labs, Menlo Park, California) can be worn for periods up to several weeks, followed by removal, and sent to a laboratory for analysis. This device can measure cumulative drug use over time but would not be suitable for roadside testing due to the lengthy time required to produce a sufficient sample and the requirement for laboratory analysis. Another sweat testing device, Drugwipe (manufactured by Securetec), has been tested on drivers in a number of European evaluations (Verstraete and Puddu, 2000) with mixed results. A major problem with sweat testing is the low concentrations of drugs/analytes detectable in sweat, producing a high variability in detection capability across individuals. Currently, there are no national standards for the

detection of drugs in sweat, and there are no certification programs for sweat testing.

Hair Testing

While the technology for assaying hair for drugs of abuse has progressed somewhat over the last 15 years, there remain many unresolved issues: for example, it is still unclear how drugs actually enter the hair. Because hair only grows at a rate of about one-half inch per month, it is not suitable for the detection of recent use. Therefore, it is highly unlikely that hair could serve as a viable specimen in DUID testing.

Urinalysis

The drug testing methodology for urinalysis is well established. With the advent of workplace testing, where large numbers of drug tests are conducted daily in the United States, urinalysis methods have become the standard by which other technologies are being compared. Drugs and drug metabolites are detectable in urine for several days after the drug has been used. This several-day window of detection can overlap with intoxication, impairment, and being "under the influence," and can extend even beyond these states of behavioral impairment. Therefore, while a positive urine test is solid proof of drug use within the last few days, it cannot be used by itself to prove behavioral impairment during a focal event. There are national standards for urine testing in place as well as national certification programs for laboratories performing forensic urine drug testing.   A number of states with per se "zero tolerance" laws are currently using urine tests to enforce their laws under which the prosecutor must show only that the driver of the car had prohibited metabolites in his/her system.

DRUG SCREENING TECHNOLOGY

As Joscelyn et al. (1980) pointed out,

In almost all most cases the analyst does not know which – if any –drug(s) are present in a body fluid specimen. Systematic analyses, called drug screens, are required. The analyst can only find those drugs his instruments can detect and identify, at concentrations within the limits of sensitivity of his methods. Because drugs number in the thousands, he will analyze specimens for those drugs of interest whose presence can reasonably be expected. Other drugs will go unnoticed. Costs of extensive drug screening and requirements for special methods to detect certain drugs or groups of drugs limit the range of drugs for which analyses are performed. (p. 87)

Joscelyn and associates then outlined the salient characteristics of analytical methods in a table reproduced below as **Table 3-1**

Table 3-1: Characteristics of a Method to Detect and Measure Drugs in Body Fluids[a]

Characteristic	Definition
Specificity	The capability of a method or technique to distinguish between individual drugs or classes of drugs.
Sensitivity	The ability of a method to detect the presence of drugs or classes of drugs.
Speed	The time from start to end of the analytical process using a method.
Simplicity .	Usually related to the speed of a method, the requirement for little training for technicians and often associated with highly automated procedures.
Reliability	The dependability of a method. Its ability to reproduce accurate and precise results day-to-day.
Accuracy	The degree to which a method produces results consistent with actual values.
Precision	The consistency with which a method reproduces results when measuring the same sample.
Economy/Cost	Economic considerations include time of analysis, number of samples processed in a single run, degree of training required of personnel, price of obtaining (and maintaining) instrumentation, price of chemicals and other reagents used in analytical procedure, and overhead of analytical laboratory or other facility.
Safety	The degree to which personnel using a procedure are exposed to risk of injury or long-term toxicity associated with chemicals required by a method.

[a] After Joscelyn, Donelson, Jones et al. (1980)

In 1980, TLC and GC were the state of the art and the most commonly used screening procedures. In 2002, most laboratories use immunoassay screening technology with GC/MS confirmation. Immunoassays are sensitive, selective, rapid and large numbers of samples can be processed simultaneously. GC/MS techniques (and sometimes tandem MS/MS) are used to separate drugs, specifically identify with the drugs's "fingerprint," and quantify the amount of the drug in the specimen. Over the last 20 years the cost of using these technologies have become affordable, and most laboratories now have the equipment, the assays and the expertise to identify the most commonly used drugs.

Over the last decade, diagnostic manufacturers have developed new immunoassays that are more specific and more sensitive to target drugs. Laboratory techniques evolving from high-volume workplace drug testing research and development have been integrated into most forensic laboratories, thus improving accuracy, reliability, and efficiency. Clearly, there have been significant improve-

ments in laboratory assays for drugs of abuse. However, the reliance solely on the forensic laboratory to assay all specimens in all cases creates a limiting factor for prosecuting DUID cases, because there are simply not enough forensic resources currently available.

Some of the most recent advances in drug testing have been the developments in the rapid point-of-collection testing products. There are at least 50 rapid point-of-collection-testing (POCT) immunoassay devices currently available on the commercial market. While most of the currently available devices are designed to test urine and can be used at a police station, some of these new devices are designed to test oral fluids and could eventually be used at the roadside.

These POCT devices could be used by police officers to routinely screen impaired driving suspects for illegal drug use and obtain drug test results immediately, as they currently do with alcohol tests. Having immediate screening results would permit the officer to confront the driver with the drug test result, and make an initial charge. Confirmation testing in a toxicology lab would generally be required. However, if the driver admits to drug use, additional laboratory testing may not be required for prosecution.

A number of these devices have been used successfully by police to test drivers for recent drug use (Buchan, Walsh, and Leaverton, 1998; Hersch, Crouch, and Cook, 2000; Verstraete and Puddu, 2000). In a series of studies funded by the National Institute on Drug Abuse, Walsh et al. (1997) demonstrated the feasibility of having police officers use urine testing devices to test DUI suspects for recent use of drugs of abuse.

NHTSA has also recently completed a project in which police officers in Houston, Texas and Long Island, New York evaluated five on-site urine testkits (Triage®, TesTcup5®, AccuSign®, Rapid Drug Screen®, and TesTstik®) with DUI suspects. The officers participating in this project were certified "Drug Recognition Experts" (DRE) who had been trained in the NHTSA-approved "Drug Recognition and Classification Program." Overall results indicated a 36% positive rate for illegal drugs (mostly cannabis, cocaine, and MDMA). GC/MS confirmation of all on-site test positives (and some negatives) indicated that the kits performed well, and the DRE officers participating in the study "favored the use of on-site devices in the enforcement of impaired driving laws" (Hersch, Crouch, and Cook, 2000).

The European Union has recently funded a major drugs/driving study called "ROSITA" (Roadside Testing and Assessment) evaluating rapid urine, sweat, and saliva POCT drug testing devices in eight European nations (Verstraete and Puddu, 2000). The principal conclusions of that two-year study were: (1) that roadside drug testing is sorely needed, and (2) that the need is so great that in some countries, police officers would rather use an imperfect device/method than wait for a more suitable one. The device evaluations in the ROSITA project indicated that, while police favored the oral fluids as the preferred matrix, "the present generation of on-site oral fluid tests are insufficiently sensitive and/or

specific to give reliable results for most classes of drugs." Sweat testing devices performed poorly. While rapid urine tests are clearly not perfect, they may be suitable for a rapid preliminary screening test. In the ROSITA device evaluations, several urine drug tests satisfied the criteria for accuracy, sensitivity, and specificity when compared with a reference method, although none scored highly for all drug categories.

THE FUTURE IN DETECTING DRUGS IN DRIVERS

Having an immediate drug test result obtained from a POCT-type test would permit the officer to confront the driver with the drug test result and make the DUID charge. At this time, however, only the urine based POCT technology appears to provide the accuracy and reliability required, and use of this technology is not yet widespread. With the advent of more "zero tolerance" laws, we may see the use of this technology grow. The development of sweat and oral fluid technology holds great promise for the field, but the most recent evaluations indicate that it may be a few more years before the desired sensitivity, specificity, accuracy, and reliability are attained.

SUMMARY AND CONCLUSIONS

For more than twenty years, medical and traffic safety researchers have been aware that the prevalence of illegal drug use among impaired drivers, especially those in motor vehicle crashes, is not negligible (Lundberg, White, and Hoffman, 1979; Williams, Peat, Crouch et al., 1985). However, the lack of forensic resources and technology to routinely and rapidly test for drugs has limited efforts to accurately document the scope of the problem or enforce DUID laws. There have been significant technological advances in drug testing technology during the last five years, but generally this new technology has not been integrated into DUID enforcement or crash investigations.

In 1980, Joscelyn and associates found that most state and local agency forensic laboratories were overworked and underfunded, and that most the drug analyses were limited to fatally injured drivers, or to those impaired driving cases where the BAC level was below the illegal limit.

In the year 2002 not much has changed. State and local forensic laboratories continue to lack sufficient resources to routinely test for drugs. As the problem of drugged driving appears to be on the increase, there is a real need for federal and state agencies concerned with traffic safety to provide additional support to enhance forensic capabilities. However, the forensic community also needs to take a look at the new POCT technology and attempt to integrate this technology with laboratory testing into a more efficient and cost-effective system. Until there is adequate capability for rapid, cost-effective drug testing, the majority of drugged drivers will not be identified or prosecuted.

4 - EXPERIMENTAL RESEARCH

INTRODUCTION

Literature documenting experimental research on drugs is reviewed in this chapter. Two general types of research are treated, (1) research conducted in a laboratory testing human performance on tasks believed to be related to driving, and (2) research conducted either in a driving simulator or on a closed course testing performance of actual driving tasks. The discussion is organized by drug class, with individual studies within a class being discussed with respect to their design, their findings, and their conclusions. Some studies compared different classes of drugs, and these studies are placed with the class that seemed to be their major focus. Classes of drugs considered are:

- Narcotics - includes natural drugs such as codeine and morphine which are constituents of opium (opiates), semi-synthetic drugs such as heroin and hydromorphone derived from opium constituents, and synthetic drugs (opiods) such as meperidine and methadone having a similar analgesic effect on the body.
- Central Nervous System (CNS) Depressants - Often referred to as "down-ers," these drugs include sedatives, hypnotics (sleep-inducing), minor tranquilizers, anxiolytics, and antianxiety medications. Specific drugs in this class include benzodiazepines, barbiturates, and meprobamate.
- CNS Stimulants - These dugs are sometimes referred to as "uppers" and reverse the effects of fatigue on both mental and physical tasks. Two commonly used stimulants are nicotine and caffeine. More potent stimu-lants include cocaine, amphetamine, and methylphenidate (Ritalin).
- Cannabis - Short for *Cannabis sativa L.*, the hemp plant, which grows wild throughout most of the tropic and temperate regions of the world. A constituent is delta-9-tetrahydrocannabinol (THC), which is believed to be responsible for most of the characteristic psychoactive effects of cannabis.
- Antidepressants - Drugs prescribed most often for clinical depression and severe cases of depression. Sub-classes include the tricyclic antidepres-sants (for example, amitriptyline and doxepin); the Serotonin-Specific Reuptake Inhibitors (SSRI) including fluoxetine (Prozac); Monoamine Oxidase Inhibitors (MAOIs), including phenelzine (Nardil); and several new drugs such as venlafaxine (Effexor) and nefazodone (Serzone).
- Antihistamines - When used to relieve or prevent the symptoms of hay fever and other types of allergy, antihistamines work by preventing the effects of a substance called *histamine*. Some of the antihistamines are also used to prevent motion sickness, nausea, vomiting, and dizziness. In

addition, since the older antihistamines may cause drowsiness as a side effect, some of them are used to induce sleep. The newer antihistamines do not produce drowsiness to any significant extent.

- Other Drugs - Consists of a few drugs not included in the above classes that have been investigated in a few individual studies. Examples are antihypertensives, antivertigo drugs, and anabolic steroids.

Laboratory studies have used a variety of tests to determine the effect of drugs on performance assumed to be related to driving. Some of the more commonly used tests are:

- Digit symbol substitution test. The subject has to substitute digits for symbols as they encounter them on a page, based on the rule that was just presented.
- Peak saccadic velocity. A measure of saccadic eye movement, that reflects the peak velocity as the eye moves from one fixation to the next.
- Critical flicker fusion test. The frequency at which a flickering light is first perceived as continuous.
- Sternberg memory test. Requires a subject to decide as quickly as possible if a projected letter/digit/word is the same or different than a small group of letters/digits/words stored in memory.
- Choice reaction time. A measure of reaction time with multiple stimuli and multiple possible responses.
- Simple reaction time. A measure of reaction time in a task that has only one stimulus (for example, a red light) and one appropriate response (for example, pushing a button).
- Time estimation. A measure of the slowed or speeded operation of mental processing as reflected in a person's ability to reproduce a given time period of several seconds.
- Serial subtraction of numbers from a predetermined number. Counting backward in fixed steps, for example, by 3s or by 7s.

Simulator studies have been conducted across a range of levels of complexity, from subjects seated in front of a screen operating simulated vehicle controls to subjects seated in a mounted module experiencing realistic dynamic motion feedback from their inputs to the simulated vehicle controls. The Daimler-Benz simulator in Germany is an example of the most advanced driving simulators and has been used in a number of studies of the effect of drugs on driving perfor-mance. NHTSA's National Advanced Driving Simulator (NADS), currently initiating operations, is another example of the most sophisticated driving simula-tors. The NADS consists of a large dome in which entire cars and the cabs of trucks and buses can be mounted. This allows the driver to feel acceleration, braking and steering cues as if he or she were actually in a real car, truck or bus.

Closed-course driving studies have typically been conducted on a road or open area closed to other vehicles. Instrumented vehicles are used, and the vehicle's actual responses to driver inputs to steering, braking, and acceleration controls are measured.

NARCOTICS

Laboratory Studies

Only four laboratory studies published after 1980 were found for this class of drugs. In the first study, Stevenson, Pathria, Lamping, et al. (1986) administered diazepam (7.5 mg) or fentanyl (a synthetic opioid, 100 micro-grams), or placebo, to 5 male and 4 female students. They measured performance on a tracometer (a driving-related task sanctioned by the National Research Council), before, 30 minutes after drug administration, and 120 minutes after drug administration. The results showed that both drugs impaired performance on four tracometer tasks (correct reaction time, non-overshoot movement time, overshoot movement time, and total response time). Interestingly, although fentanyl has a shorter half-life time than diazepam (2 hours vs. 9 hours), in general, the impairments with fentanyl increased after 2 hours, whereas the impairments with diazepam de-creased (indicating lack of relationship between drug plasma level and size of effect).

More recently, Kubitzki (1997) compared the performance of 22 patients 25-45 years old who had been undergoing methadone treatment for 1-5 years, with the performance of matched (for age, sex, and education) control subjects. The methadone dosage levels of the subjects was not indicated, though presumably subjects were tested at their therapeutic doses. The groups were compared on several cognitive and psychomotor tasks, including tracking, reaction time, "cognitive perceptual speed" and driving on a closed course. The results failed to yield any significant differences between the two groups; leading the author to conclude that there is no performance-based reason to preclude such people from driving at the dosages tested.

In their evaluation of the correlation between drug presence and various signs and symptoms, Zancaner, Giorgetti, Dal Pozzo, et al. (1997), examined the blood or urine of 480 Italian drivers stopped by police for DWI. Although the frequen-cies of the different drugs are not reported in their paper, they did find a few suspects with opiates, and noted that relative to unimpaired people, a "high percentage" of them had poor coordination, especially as observed with the finger-to-nose test.

The most recent analysis of codeine impairment was reported by Compton, Shinar, and Schechtman (2000), who analyzed its effects on signs and symptoms included in the Drug Evaluation and Classification program (DEC). The only

statistically significant effect they found was a reduction in pupil size, both in the light and in the dark.

In summary, although the data related to driving-related skills is sparse, narcotics can impair some behaviors, but further studies are needed to determine their effect on motor coordination, reaction time, and movement control.

Closed-course and Driving Simulator Studies

We found no recent closed-course or driving simulator studies of acute effects narcotic drugs. However, in an earlier study, Linnoila and Hakkinen (1974) studied the behavior of Finnish professional military drivers, 19-22 years old, in a driving simulator. Different groups of 10 subjects each were provided with either no drugs, alcohol, diazepam (10 mg), codeine (50 mg), alcohol+codeine, or alcohol+diazepam. The driving task started 30 minutes after drug/alcohol administration. Results showed that the number of "collisions" was greatest with codeine alone (more than with alcohol or with alcohol+codeine). The drivers under the influence of codeine and codeine+alcohol also went off the road more often and neglected more of the instructions than the control groups. Thus, codeine definitely impaired driving, but the drug-alcohol interaction was not simple.

An interesting recent study addressed the chronic use of narcotics as a treatment for pain (Galski, Williams, and Ehle, 2000). Sixteen patients with chronic nonmalignant pain on Chronic Opioid Analgesic Therapy (COAT) underwent a comprehensive off-road driving evaluation using several measures believed to be predictive of on-road driving performance. The evaluation consisted of a pre-driver evaluation, a simulator evaluation, and behavioral observation during simulator performance. Patients in the COAT group were compared to a historical control group of 327 cerebrally compromised patients (CComp) who had undergone the same evaluation and then passed an on-road, behind-the-wheel evaluation (n = 162) or failed the behind-the-wheel evaluation (n = 165). The results revealed that COAT patients generally outperformed the CComp patients as a group. Notably, COAT patients had a relatively poorer performance than CComp patients on specific neuropsychometric tests in the pre-driver evaluation; however, the differences were not statistically significant. Behaviorally, COAT patients were generally superior to CComp patients, but COAT patients had greater difficulty in following instructions, had a tendency toward impulsivity, and were similar in these respects to the Ccomp subjects who failed the behind-the-wheel evaluation. The authors concluded that COAT did not appear to significantly impair the perception, cognition, coordination, and behavior measured in off-road tests.

CENTRAL NERVOUS SYSTEM DEPRESSANTS

Benzodiazepines

The benzodiazepine family of depressants are used therapeutically to produce sedation, induce sleep, relieve anxiety and muscle spasms, and to prevent seizures. The most common side effect of benzodiazepines is sedation, due to their CNS depressant action (Kunsman, Manno, Przekop et al., 1992). Benzodiazepines are distinguished from each other in terms of the duration of their effects. Long half-life benzodiazepines sustain their effects – and their side effects - for more than nine hours. Examples are alprazolam (Xanax), chlordiazepoxide (Librium), clorazepate (Tranxene), diazepam (Valium), halazepam (Paxipam), lorazepam (Ativan), oxazepam (Serax) and prazepam (Centrax). Shorter half-life benzodiazepines typically reach their peak within two to three hours and include estazolam (ProSom), flurazepam (Dalmane), quazepam (Doral), temazepam (Restoril) and triazolam (Halcion).

Laboratory Studies. A large number of pertinent laboratory studies have appeared since 1980. Rothenberg and Selkoe (1981) measured saccadic eye movements in response to a dot that jumped 2-36 degrees nasally from the center of the visual field, in a random fashion. Performance of 6 healthy volunteers was measured 75 minutes after administration of 0, 5 or 10 mg diazepam. Bittencourt, Wade, Smith, and Richens (1981) performed a similar study of eye movements, both studies finding an impairment in visual search performance.

Also in 1981, Landauer (1981) published a review of the literature in which he concluded that no studies clearly indicated whether orally administered diazepam adversely affects the ability of a patient to drive a car. He noted that while it is preferable for anxious, aggressive, or depressed patients not to drive, diazepam tends to relieve these symptoms, and its use by such patients should not lead to an automatic prohibition of car driving

However, Soames (1982) disagreed with Landauer's contention, asserting that the bulk of evidence suggests that diazepam *is* harmful to driving ability, even in appropriate patient populations, and that the detrimental effects of alcohol on driving ability are also exacerbated by diazepam. He recommended that patients taking diazepam should avoid driving, especially if they have taken any alcohol.

Parrott, Hindmarch, and Stonier (1982) administered either clobazam, nomifensine (an antidepressant), a combination of the two, or placebo, five times over a period of 3 days each. They tested the effect of the drugs on the performance of twelve female volunteers of age 28-46 immediately after the 5th administration or later in the afternoon. No effects were found (relative to placebo) on any of the performance measures for all three drug conditions. The authors noted that the results are quite consistent with those of previous studies, in so far as they suggest

that there is an adaptation effect in response to chronic administration of these drugs.

Spinweber and Johnson (1982) used a between-group design to evaluate the effects of 0.5 mg triazolam on performance on various psychomotor tasks. Their subjects were 20 male poor sleepers, an average age of 21 years old, who were awakened 1.5, 3, and 5 hours after nighttime drug administration, over a period of 6 nights. They found performance was worst at the short intervals of 1.5 and 3 hours after drug administration.

Griffiths, Bigelow and Liebson (1983) administered low and high doses of diazepam and pentobarbital to 12 men with a history of sedative drug abuse, over a period of 5 days, followed by 10-14 days of placebo. They found that both diazepam and pentobarbital produced dose-related deteriorations in choice reaction time and daytime sleeping. However, only diazepam produced dose-related decreases in staff rating of patients' mood and social interaction, and increases in staff rating of hostility and unusual behavior. The maximal drug effect for both dosages appeared 2 hours after drug administration.

In his analysis of the effects of different drugs on attention tasks, Moskowitz (1984) briefly mentions an unpublished study in which his subjects performed a central tracking task and a peripheral target detection task after ingesting flurazepam (0, 15, 30, and 55 mg). There were dose-related long-term impairments (up to 12 hours after drug intake) of flurazepam on both the central tracking task and the peripheral target detection, and the magnitude of the effects increased as the attentional level of the central task increased. According to Moskowitz, the drug-impaired subjects' ability to divide their attention, caused them to disregard one of the two tasks – with different subjects disregarding either the central or the peripheral task. Thus, the impairing effect was most noticeable when the performance scores from the two tasks was combined.

Roache and Griffiths (1985) evaluated the effects of 0.5, 1.0, 2.0, and 3.0 mg triazolam (Halcion) and 100, 200, 400, and 600 mg pentobabital (Nembutal – a standard barbiturate hypnotic) on 8 male drug abusers, 20-40 years old. Performance was measured 1, 2, 3, 4, 6, 8, 12, and 24 hours after administration. They found dose-related and time-related effects on most subjective measures, performance measures, and staff ratings of observed effects. The effects peaked at 2-3 hours for both drugs.

Roth and Roehrs (1985) observed that studies of so-called hypnotic drugs have generally focused on the effects the drugs have on sleep, but that it is now clear that they also have effects that can extend beyond the usual sleep period. These residual effects of hypnotics are assessed by studying the effects of these drugs on performance. Their paper discusses the issues critical to evaluating studies of the effects of hypnotics on performance, concluding that dose and half-life are important variables in determining the degree to which these daytime effects occur following nighttime use. However, the authors found several issues still unresolved, *viz.*:

- whether residual effects persist with chronic use,
- whether any specific skill may be more or less sensitive to residual effects, and
- the degree to which the decrements occur in different populations.

In a recent paper, Vera and associates (2001) compared the residual effects of benzodiazepines on attention and psychomotor performance with the effects of certain non-benzodiazepine compounds on these parameters. Their concern was the residual effects on diurnal wakefulness in healthy volunteers after nocturnal administration of a single dose of diazepam (10 mg), zolpidem (10 mg), zopiclone (7.5 mg), gamma-amino-beta-hydroxybutyrate (GABOB) (500 mg), or placebo. The drugs were given at 10:00 p.m., a half-hour before bedtime. The morning after dosing, psychomotor performance was measured using a simple reaction time task, with two stimulation patterns (isochronus and stochastic). The results indicated no residual effects on reaction time after diazepam, zopiclone, and zolpidem intake. In comparison to its baseline, only GABOB produced a marked decrease in the isochronus reaction time 9 hours after its administration and produced no significant change in stochastic reaction time. The authors concluded that residual impairment on reaction time following intake of hypnotics should be considered on the basis of the stimulation pattern used (stochastic vs isochronus).

In another paper, Landauer (1986) revisited the issue of driving by patients who receive benzodiazepine tranquilizers, asserting that groups that believe that such patients should be prevented from driving a car disregard the fact that there exists no study to show that these drugs are a causal factor in crashes. His paper reviewed the effect of diazepam, one of the older compounds. The author concluded that some studies have shown that performance on psychomotor skill tests are at times affected by diazepam medication, a few studies report a decrement in performance, some found an improvement, but the results of the vast majority of studies are inconclusive. Landauer found that if detrimental effects do occur, they usually appear during the early stages of medication and when high doses are given. He states that many published studies suffer from methodological errors, and that there is little evidence that the tests used by the different teams measure the same aspect of behavior. He also concluded that there is insufficient epidemiologic data to adequately describe the relationship between all drugs and road safety, and notes that large-scale field studies have not been attempted with any pharmaceutical drug.

Stevenson, Pathria, Lamping, et al. (1986), administered diazepam (7.5 mg), fentanyl (a synthetic opiod, 100 micro-grams), or placebo, to 5 male and 4 female students. They measured performance on a "tracometer" (described only as "an NRC-sanctioned driving related task"), before drug administration, 30 minutes after drug administration, and 120 minutes after drug administration. Results showed that both drugs impaired performance on four tracometer tasks (correct

Moser, Macciocci, Plum, and Buckmann (1990) administered 2 and 4 mg flutoprazepam to18 healthy 20-45 years old volunteers, in a cross-over design, and tested reaction time for "simple and complex shape recognition" (not defined further). They found that, relative to performance before drug dosing and relative to performance with placebo, performance 2.5 hrs after drug administration (time of peak plasma level) was significantly impaired, but only with the high 4 mg dose level.

Fisch, Baktir, Karlaganis, et al. (1990) studied the effects of 0.25 mg triazolam on pursuit rotor performance of 9 elderly and 9 middle-aged healthy volunteers, before, and 2 hours after drug ingestion. Age-related differences were obtained under the control condition, and they increased after drug ingestion.

Johnson, Spinweber, and Gomez (1990) evaluated the effects of 250 mg caffeine the morning after intake of either 15 or 30 mg flurazepam (with long half-life), 0.25 or 0.50 mg triazolam (with short half-life), or placebo at bedtime the night before the testing. The subjects were 80 healthy male volunteers, with mean age of 20.3 years. Performance measures were taken before and after treatment. The results showed that the drugs caused a feeling of sleepiness, and caffeine counteracted the effects of these feelings. Despite the differences in the subjective scores, no consistent significant differences were found between any of the groups on any of the performance measures. The authors noted that their failure to find improved performance after caffeine ingestion "joins the growing list of inconsistent results" (p. 165). However, the fact that they also failed to find differences between the placebo and the drug dose groups suggests that their measures in general (for an unknown reason) were not very sensitive to the drug effects as well.

Leigh, Link and Fell (1991) administered 2.5 mg lorazepam to 12 male volunteers 19-46 years old in a within-subject single-blind study design. They evaluated the subjects' subjective feelings and psychomotor performance before drug administration and over a period of 1.5 hours to 24 hours after administration. They found time-related impairments on almost all measures of subjective feelings of drowsiness, lethargy, clumsiness, and related feelings, as well as decrements in a number of the performance measures, including choice reaction time, motor control and coordination, and rapid information processing.

Preston, Wolf, Guarino, and Griffiths (1992) compared the effects of three sedatives: 1 and 4 mg lorazepam (benzodiazepine anxiolytic), 2.5 and 9 gram methocarbamol (central muscle relaxant), and 100, 200, or 400 mg diphenhydramine (antihistamine with sedative properties). The drugs were given in dosages 2-8 times the recommended therapeutic doses to 14 male regular drug abusers, ages 20-38. The use of the high doses was based on the assumption that recreational dosages are much higher than therapeutic doses. Testing was performed for 5 hours after ingestion. The researchers found both dose-related and time-related drug effects on performance and sensation of drug effects, with maximal effect at approximately 2-3 hours. Performance on psychomotor tasks deteriorated for all

three drugs, especially at the high dose level. At the high dose level, both diphenhydramine and lorazepam impaired performance on choice reaction time to circular lights, balance on one-leg-stand, digit symbol substitution test, and short-term recall for numbers and pictures. Methocarbamol impaired performance only on the balance test, and the digit symbol substitution test. These results demonstrate that, with sufficiently high dose levels, impairments can be observed, but with dose levels typical of therapeutic doses, the impairments can be negligible.

Kunsman, Manno, Manno, et al. (1992) administered 15 mg temazepam and alcohol that yielded average levels of .08, .07, and .04 BAC, at the times of testing (30, 90, and 150 minutes, respectively, after the ethanol-drug intake). They found that, in combination, temazepam+alcohol impaired divided attention, tracking, and reaction time over a 3-hour period. Tapping rate was not significantly reduced by either drug alone or by their combination. No temporal effects or plasma concentration relationships with impairment were obtained. Divided attention was also impaired by temazepam alone and by alcohol alone, but pursuit tracking and choice reaction time were not impaired by each drug alone. The authors also noted that "when each drug was given alone, performance was highly variable. Some subjects were impaired, some subjects improved, and some subjects showed no effect versus placebo" (p. 610). Individual differences in rate of absorption of the drugs may also account for the lack of temporal effect. This is because at any given time concentration levels were still increasing in some subjects, decreasing in some subjects, or leveled off in others.

Based on their own study (above) and those of others, Kunsman, Manno, Przekop, et al. (1992) reviewed the effects of benzodiazepines in general, and temazepam in particular. Their conclusions with respect to the following psychomotor tasks were:

- Simple reaction time is slowed by therapeutic doses as long as the testing is done within 1-3 hours of the ingestion. With long-life benzodiazepines, the impairment may persist over the night. However, continued repeated administration eventually causes resistance (adaptation) to the impairing effects.
- Choice reaction time is affected in a manner similar to simple reaction time, as long as the tests are done within the half-life time frame of the drug. However, some studies obtained an impairment of simple reaction time and not on choice reaction time, others showed effects on choice reaction time and not on simple reaction time, and most studies showed an impairment on both.
- Most studies show impairment on the Digit Symbol Substitution Test for hypnotic therapeutic and anxiolytic doses, and show that impairment persists as long as 6-8 hours. However, studies of repeated evening administrations generally show no effects the following morning, indicative of an adaptation effect. The dose response relationship of these

impairments is much more regular than that observed for simple reaction time or choice reaction time.

- The Critical Flicker Fusion Test has not been used as much as the above tests, but when it has been used, impairments within 5-8 hours of administration have been shown. In general, similar results were obtained with different types of benzodiazepines.

- Tests measuring the maximum number of taps within a short time have shown effects of the drug, but only at high dosages, with levels much higher than needed to show impairment on other performance measures such as reaction time and tracking. This suggests that diazepine-induced impairment is probably due to perceptual/cognitive impairments rather than motor impairments.

- Tracking performance is generally poorer with diazepams, but the impairment is typically limited to 2-4 hours after drug administration.

- With respect to divided attention, most of the studies reviewed used tracking and reaction time as the two tasks that had to be time-shared. Performance decrements in either of the tasks have been found for both acute and chronic administration of benzodiazepines. In this respect, divided attention is more sensitive than the previous tests that were typically not sensitive to chronic administrations.

- A test of visual scanning, the letter cancellation task, shows performance decrements 1-3 hours after administration.

- Performance on simple arithmetic and digit-recall also deteriorates after benzodiazepine administration.

Kunsman, Manno, Przekop, et al. (1992) also focused their attention on the specific benzodiazepine, temazepam, a drug typically taken at night before going to sleep. Multiple studies that evaluated temazepam's effects on the following morning generally failed to show decrements in psychomotor performance with low dosages. However, with high dose levels of 30 mg, impairments in a number of tasks have been found.

Martin, Siddle, Gourley, et al. (1992) investigated the effect of temazepam on P300 (a brain signal that indicates recognition of an event) in a paradigm that may be relevant for traffic behavior. Because crash scenes have not been used previously in P300 research, Experiment 1 (n=8) examined whether the P300 elicited by safe traffic scenes and scenes of imminent traffic crashes were sensitive to the probability of crash occurrence. The type of stimulus to which subjects responded (pictures of imminent crashes or safe traffic scenes) was crossed with the probability (0.1 or 0.5) of the relevant event. The results indicated that P300 amplitude increased with decreasing probability of the relevant stimulus. Experiment 2 (n=12) employed a drug treatment (10 mg temazepam) and a placebo treatment (100 mg Vitamin E). Generally, the ingestion of temazepam decreased P300 amplitude and increased P300 latency at all sites. Reaction time, on the

other hand, was not influenced by drug administration. The data demonstrate the clear effect of minor tranquilizers on the psychological processes associated with P300.

Evans, Troisi, and Griffiths (1994) compared the effects of alprazolam (0.5, 1.0, 2.0 mg) and with those of a non-benzodiazepine antidepressant (tandospirone, from the azapirone family, 40, 80, 160 mg) on 14 male habitual drug abusers, in a double-blind cross-over study. Both drugs showed dose-related and time-related effects, but the impairments with alprazolam were much more severe. Alprazolam had significant effects on choice reaction time to circular lights, digit symbol substitution test, balance (one-leg-stand for 30 seconds), and a number entering and recall test (a task where 8-digit numbers on screen had to be entered on computer and then recalled either immediately or after 10 seconds). Performance on all tasks with the 2.0 mg dose was approximately 50% of the pre-drug dose levels (except for circular lights where it was 70%). Interestingly, the stronger the alprazolam dose, the more the subjects said they liked it and the more they said they would be willing to pay for it.

Suzuki, Uchiumi, and Murasaki (1995) compared the effects of 0.8 mg alprazolam with those of DN-2327 – a partial diazepine receptor agonist – in doses of either 2 or 3 mg. Their subjects were 12 healthy males, with an average age of 41 years old. The design was a crossover double blind, with 2 weeks between sessions to wash out previous drug effects. The performance measures included a letter cancellation task, a visual vigilance task (in which a recurring pair of dots 48 mm apart on a computer screen were occasionally displaced to 60 mm apart), and a Sternberg's memory task with a memory set ranging from 1 to 6 digits. Performance was most impaired on the high dose DN-2327 followed by alprazolam and 2 mg DN-2327, which generally did not differ significantly from each other. The results indicated the difference between the drugs is in their effects on the information encoding process rather than on the central, decision-making, processing stage.

Fafrowicz, Unrug, Marek, van Luijtelaar, Noworol, and Coenen, (1995) tested the latency of saccadic eye movements (simple reaction time) in response to a target light that appeared either while the fixation light was on (overlap condition) or 200 milliseconds after it disappeared (gap condition). In a within-subject design, they tested 5 volunteers 30 minutes after taking either placebo, 5 mg buspirone (a non-sedative anxiolytic), or 5 mg diazepam. They found that diaze-pam – but not buspirone increased simple reaction time, and the effect was the same in the gap and overlap condition. Their conclusion was that diazepam slows down the shifting of attention or the engagement of attention with a new target rather than the first step of the attention – disengaging attention from the existing target. As such it would be detrimental especially in attending to peripheral targets under conditions of overload, such as in driving in congested traffic. Possibly, the prolonged latencies may be due to the sedative vigilance-lowering effect of diazepam.

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Kelly, Foltin, Serpick, and Fischman (1997) evaluated the effects of acute administration of different doses of alprazolam on 6 healthy volunteers, in a within- subject design. There was a dose-dependent drop in performance on most measures, but of the four dose levels studied (placebo, 0.25, 0.5, and 1.0 mg), only the 1.0 mg dose had significant effects. The effects were found on the digit symbol substitution test, time estimation (based on a time production test where subjects had to press a button every 45 seconds or more), short-term memory (number recognition test where subjects had to compare a list of digits to one stored in memory), and two measures of learning ability. The authors note that these results are consistent with those of previous studies with alprazolam. Kelly and associates also noted that studies using the same measures obtained different patterns of impairments with amphetamine.

The most extensive and recent summary of the relevant side-effects of benzodiazepines is probably that of Berghaus and Grass (1997), who summarized over 500 experimental results of studies that related performance on driving-related psychomotor and perceptual tasks to benzodiazepine impairment. They found a clear-cut relationship between the serum concentration and the percent of studies that obtained a significant effect. Note, though, that multiple results were recorded for each study, so these are not independent "results." Similar relation-ships were obtained for other benzodiazepines such as temazepam, flunitrazepam, flurazepam, alprazolam, bromazepam, diazepam, oxazepam, and lorazepam. One exception was clobazam for which significant effects were first obtained at the very high serum level of 400 ng/ml. Berghaus and Grass also found that the percent of studies obtaining an impairment was much higher (by as much as 30%) when the serum concentration was measured during the absorption phase, than when it was measured during the elimination phase. We note that this effect is similar to that obtained for alcohol, but it is much stronger with benzodiazepines.

We note that Berghaus and Grass' summary masks some of the perplexing discrepancies that are often obtained between similar drugs or similar samples. For example, an earlier review of studies that compared different types of depres-sants – such as barbiturate hypnotics, non-barbiturate hypnotics, and tranquilizers - showed that often the results with the same dependent measure conflicted. Some of the differences among the studies that could have been responsible for these discrepancies include variations in experimental design (for example, within vs. between subjects), drug dose, and drug-test interval.

In a related study, Berghaus and Friedel (1997) analyzed the percent of studies showing impairment as a function of time since administration of benzodiazepine. While studies with clobazam (at 10 or 20 mg) and temazepam (10 mg) generally yielded no significant impairments at all, most studies with other benzodiazepines showed impairments for up to 5-6 hours (midazolam, diazepam, oxazepam, triazolam, and lormetazepam), and studies with some high-dose long-life benzodiazepines [nitrazepam (10 mg) flunitrazepam (2 mg), and flurazepam (30 mg)] showed significant impairments lasting as long as 18-24 hours.

As part of an evaluation of the Drug Evaluation and Classification program (DEC), Compton, Shinar, and Schechtman (2000) compared the effects of different drugs on performance of the standard DEC tests. Using alprazolam as a representative depressant drug, they found that it produced effects similar to those of alcohol: nystagmus, poor performance on all balance tests (one leg stand, finger-to-nose test, and walk-and-turn test), slowed reaction to light, and poor ocular convergence to nearby objects.

In summary, despite significant differences among the individual benzodiazepines, they generally impair performance on most performance tasks, in particular those that tap visual encoding of information (such as attention, vigilance, visual search, peak saccadic velocity, and critical flicker fusion), and short-term memory (such as digit symbol substitution test, memory scan, recognition memory, and serial subtraction). However, some non-sedative anxiolytics (such as buspirone, clobazam and temazepam) do not seem to impair performance on any of the driving-related functions that have been studied.

Closed-course and Driving Simulator Studies. In an earlier study, Linnoila and Hakkinen (1974) investigated the behavior of Finnish professional military drivers in a driving simulator. Different groups of 10 subjects each were provided with either no drugs, alcohol, diazepam (a long-life benzodiazepine) (10 mg), codeine (50 mg), alcohol+codeine, or alcohol+diazepam. The driving task started 30 minutes after drug/alcohol administration, and performance was measured in terms of simulated collisions and frequency of going of the road. But an interesting side effect was noted in terms of following instructions, which was worst for the drivers impaired by alcohol alone. A smaller effect of neglecting instructions was noted for those dosed with diazepam. Interestingly, the effect of the combination diazepam+alcohol was also smaller than the effect of alcohol alone. The drivers who received diazepam had significantly more collisions but did not go off the road any more often than those without any drug. As expected, drivers with diazepam+alcohol had more collisions and more instances of going off the road than either the diazepam-only group or the alcohol-only group. In fact, none of the diazepam only drivers went off the road. Thus, it appears that while diazepam may not impair cognitive functions involved in following instructions, it does affect vehicular control, and the effect is at least additive with alcohol. Interestingly, in another simulation study, impairments were noted after 12 hours with long-acting flurazepam, but not with the short-acting drugs for which no effects were noted at all (Willumeit, Ott, and Neubert, 1984). Together, the two studies imply that if benzodiazepines impair driving, it is more likely that it is only the long-life benzodiazepines that do so.

Hobi, Kielholz, and Duback (1981) examined the effect of bromazepam on fitness to drive. On 3 days (1, 8, 15) the acute (on day 1) and subacute (days 8 and 15) effects of bromazepam on variables of driving ability were studied in 55 young male medical students, randomly divided into 3 groups (placebo, 1.5 mg,

3.0 mg). The drug was well tolerated (no notable side effects). Dose-effects showed trends in group 3 (3.0 mg) with a stronger subjective impression of performance impairment which was, however, not confirmed by objective performance assessment, although time of reaction to optical stimuli was significantly longer after the 3 mg dose. In the discussion, it is pointed out that the results of this type of study in healthy subjects can only be regarded as indicative.

Moskowitz and Smiley (1982) studied the effects on driving skills of buspirone and diazepam, singly and in combination with alcohol. Three groups of 16 subjects each (8 men and 8 women) received either 20 mg of buspirone, 15 mg of diazepam, or placebo daily for 9 days. On day 9 they also received alcohol (men, 0.85 g/kg; women, 0.72 g/kg[2]). On days 1, 8, and 9, subjects were tested on a driving simulator and given four sessions of divided attention tasks examining tracking and visual search performance. Extensive evidence of performance impairment associated with diazepam contrasted with improved performance under chronic buspirone treatment. Alcohol effects were additive.

Betts and Birtle (1982) noted that most drugs that affect the central nervous system impair driving, at least temporarily, and that hypnotic drugs of the benzodiazepine group have some "hangover" effect next morning and have been shown to impair performance in (experimental) psychomotor tasks, though the degree of impairment depends on the dose of the hypnotic, its plasma half life, and individual variability. However, they found no evidence that other researchers had looked at the effect of these drugs on actual driving and devised an experiment to do so. They chose a drug with a relatively short half life, temazepam, and one with a longer one, flurazepam. After testing subjects' ability to negotiate a path through cones on a closed driving course, the authors concluded that a single nighttime dose of both hypnotics degraded driving behavior enough to create increased crash risk.

Willumeit, Neubert, Ott, and Hemmerling (1983) investigated lormetazepam, then a new benzodiazepine derivative, in a driving simulator trial and compared it with placebo and flurazepam. Twelve healthy subjects participated in this double blind, crossover study. The aim of the investigation was to estimate any negative effects on traffic performance after subchronic (7 days) ingestion. The results indicated that lormetazepam, even in relatively high doses, does not significantly affect reaction times compared with placebo. Flurazepam, on the other hand, significantly prolonged the general reaction time to signals presented by the driving simulator. Driving performance was significantly worse after flurazepam than after lormetazepam. The cardiovascular functions were influenced neither by the subchronic ingestion of lormetazepam nor by flurazepam,

The same authors (1984) recruited 16 healthy volunteers of a mean age of 26.4 years to participate in a driving simulator test in an eightfold crossover study

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[2] This would amount to about 2.2 ounces of alcohol for a 160 pound man and about 1.4 ounces for a 120 pound woman.

under double-blind conditions. The additional influence of alcohol was tested acutely after a single administration of 2 mg lormetazepam, a new, highly effective derivative from the benzodiazepine class, 10 mg mepindolol sulphate, a new beta blocker without sedating properties, and 10 mg diazepam. All drugs were compared with placebo and the test was performed 1, 2 and 3 hours after oral intake. The aim was to investigate particularly the risks relevant in road traffic caused by simultaneous intake of these substances with alcohol. For this purpose, besides the driving simulator, an accurate reaction test and self-rating scales were used, the latter in order to assess subjective stress and anxiety levels. Lormetazepam, due to its strong sedating property, showed a reduction in driving performance and an increase in reaction time and pulse rate as compared with placebo, and these effects were highly potentiated by alcohol. Mepindolol sulphate expectedly reduced pulse rate when compared with placebo, otherwise there were no significant differences. Diazepam, like lormetazepam, caused a reduction in driving performance and reaction capacity and an increase in pulse rate compared with placebo, but the intensity and duration of the effect were less than with lormetazepam and did not reach statistical significance. No significant potentiating effects were observed after the application of alcohol.

Ellinwood and Heatherly (1985) noted that the adverse effects of minor tranquilizers, and more specifically, benzodiazepines, on psychomotor and cognitive performance have been documented repeatedly over the years, and epidemiological studies have provided sufficient evidence of their role in traffic crashes. These studies indicate that drug plasma level (DPL) is insufficiently correlated with impairment and that other factors need to be considered in determining the impairment vulnerability.   They reviewed several sources of individual variability, particularly as they relate to differential impairment effects. They found that these sources include such factors as acute peak effects, acute tolerance, chronic tolerance, benzodiazepine receptor affinity and individual sensitivity, and concluded that these factors need to be examined before quantification of DPL is introduced as a criterion for driving under the influence. They also concluded that behavioral testing itself may become the critical means of assessing drug- and/or drug with alcohol-induced driving impairment if acceptable standardized procedures can be developed. They noted the rapid onset of impairment associated with acute effects of more lipid-soluble drugs.

The validity of simulated driving, relative to real driving was directly tested by Laurell and Tornros (1986). They tested 18 healthy volunteers, 20-34 years old, in the morning after 1 and 3 nights of taking 0.25 mg triazolam (short-life benzodiazepine, with a half life of 2.3 hours) or in the morning after 1 and 3 nights of taking 5 mg nitrazepam (long-life benzodiazepine, with a half-life of 29 hours), or placebo. The performance tests consisted of both simulated monotonous driving and real driving on the morning after drug administration. In the simulated driving, the subjects had to drive a monotonous road and respond to emergency situations, and performance was measured in terms of reaction time. In the real

driving test they drove within a lane of cones and had to switch lanes in response to a sudden obstacle, and the dependent measure was the number of cones knocked over. Significant drug effects were obtained only in the simulated driving and only for the long-life nitrazepam. These results suggest that their simulated driving task was either more demanding than their real driving task or that the drivers were less concerned about their actions in the simulator than about the actual cost of errors in real driving. Since the tasks were quite different, both factors may have contributed to the performance difference.

O'Hanlon and Volkerts (1986) described the most recent of several related studies of the residual effects of hypnotic drugs on actual driving performance that have been conducted using a standard approach. In it, 12 female insomniacs and hypnotic users acted as subjects. They were treated in two separate series with placebo for 2 nights, then hypnotic medication for 8 nights followed by placebo again for 3 nights. In one series, the medication was nitrazepam (10mg) and in the other, temazepam (20 mg). Eleven subjects completed both series in a double-blind, crossover (with respect to drugs) design. Their driving performance was repeatedly tested on a 100 km primary highway circuit, in normal traffic, during both the morning and afternoon (10-11 hours and 16-17 hours after drug and placebo ingestion, respectively). Nitrazepam but not temazepam significantly impaired driving performance, the difference lasting throughout the active medication period. These results along with those obtained in the earlier studies are compared to show degrees of driving impairment which follow the use of various hypnotic drugs.

Linnavuo, Ylilaeaekkoelae, Mattila, et al. (1987) developed and tested a computerized device for simultaneous measurement of coordinative and reactive skills related to driving. The experiment involved two consecutive trials of psychoactive agents in healthy volunteers. The test system was comprised of a vehicle, a driving computer, and the programming and measurement computer. The computerized driving program projected to a color TV screen a winding road, and the driver had to keep the car on the road by turning the steering wheel. The driving proceeded at a fixed, fairly rapid rate for 5 minutes, and the number of tracking errors (deviations from the road) as well as the tracking percentage (relative length of the track driven off the road) were computed separately for both halves of the track. During the latter half of the track, 60 visual or/and sound stimuli were given in random order, and the driver had to respond to them by pressing a button or by pushing a foot pedal. The number of reaction errors and cumulative reaction time were recorded. The program also provided a histogram that related the number of deviations from the road to their duration, enabling a visual judgement of the severity of errors. Matched versions (mirror image, reverse direction) of tracks of varying severity were offered to reduce learning effect during the trial. When testing the device in two placebo-controlled double-blind and crossover trials, a considerable practice effect on tracking and reaction strategies took place, but after proper training, the baselines remained reasonably

stable. In spite of the practice effect, an impairment of coordinative skills by lorazepam 2.5 mg or by diazepam 15 mg was demonstrated whereas ethyl alcohol 0.8 g/kg impaired reactive skills more than eye to hand coordination. Additive drug-drug and drug-alcohol combined effects were also found.

In a later study similar to their 1986 study cited above, Tornros and Laurell (1990) evaluated the effects of 2 mg flunitrazepam, 30 mg flurazepam, 0.5 mg triazolam, and placebo on the fourth morning following four nightly drug inges-tions. The subjects were 24 healthy, moderate-drinking, Swedish volunteers, and the design was a double blind, randomized crossover. The subjects' task was to drive as fast as possible through a demanding 20 km course in a moving- base driving simulator. Following the test, they were given alcohol, and when the BAC level reached .05, they were tested again. The dependent measures were average speed and number of "crashes." Alcohol had an additive effect on speed, increasing average speed for all drugs. Before intake of alcohol, speed was lowest and crashes were highest with flurazepam. The other two drugs yielded similar speeds to those of placebo, but lower crash rates.

Brookhuis, Volkerts, and O'Hanlon (1990) assessed the residual effects of lormetazepam 1 mg and 2 mg in soft gelatine capsules on driving performance and compared the effects to those of flurazepam 30 mg, which is also a powerful hypnotic, but possesses a far less favorable pharmacokinetic profile with a long-acting sedative metabolite. Driving performance was tested 10 to 11 hours and 16 to 17 hours post administration, after 2 days on placebo (baseline), and 2, 4 and 7 days of drug treatment (active), and after 1 and 3 days following the resumption of placebo (washout). The driving test consisted of operating an instrumented motor-vehicle over a 72 km highway circuit in light traffic. Flurazepam 30 mg significantly impaired the ability to control the lateral position of the vehicle compared to placebo baseline measurements. The degree of impairment was substantial in the female subjects and was greater in the morning than in the afternoon. Lormetazepam 1 mg showed no residual effect on driving perfor-mance. Lormetazepam 2 mg impaired driving performance to some extent on the following morning, 10 to 11 hours post administration, but no residual effect was found in the afternoon. All drugs improved sleep quality and prolonged sleep duration to more or less the same extent.

O'Hanlon, Vermeeren, Uiterwijk, et al. (1995) studied the effects of benzo-diazepine (diazepam, lorazepam) and benzodiazepine-like anxiolytics (alpidem, suriclone) and a 5-HT-3 antagonist (ondansetron) on actual driving performance in three double-blind, placebo-controlled studies. Subjects were healthy volun-teers in two studies and anxious patients in the third. Treatments lasted for 8 days. Standardized testing occurred within the first full day and on the last day of treatment. No important differences existed between volunteers' and patients' baseline and/or placebo performances, and both groups responded similarly to comparable drugs/doses. Benzodiazepine and benzodiazepine-like anxiolytics

produced marked and pervasive driving impairment, which lasted throughout treatment; but ondansetron produced no impairment.

O'Hanlon (1984) also evaluated drug effects on actual driving performance in a series of three earlier studies. His subjects drove a 100 km at 95 km/hr on a 50 km route while their lateral position in the lane was monitored. The primary difference among the three studies was the drug under investigation. In all studies, subjects served as their own controls (with placebo). The first study was conducted on 24 female former users of hypnotic drugs, and the study's drugs were flurazepam and secobarbitone. The second study was conducted on 16 female former drug users and the drugs evaluated were loprazolam and flunitraze-pam. The third study included 20 healthy males, and the drugs evaluated were amitriptyline, doxapine, mianserin, and opiates. The three experiments demon-strated that the standard deviation of the lateral position in the lane was a sensitive measure of impairment from doxapine (25 mg three times daily), mianserin (10 mg 3 times daily), and amitriptyline (25 mg 3 times daily). Also, relative to placebo, there was also an excellent power function fit between loprazolam concentration and standard deviation of the lateral position. However oxaprotiline had no effect on lateral control.

In another earlier study, O'Hanlon, Haak, Blaauw, and Riemersma (1982) had 9 police driving instructors drive twice in succession on a 50 km highway loop in Holland, in the late evening hours under 4 different conditions - 10 mg diazepam, 5 mg diazepam, placebo, and nothing – and once at 1:00 AM. Thus, the drug effects could be compared to three control conditions: late evening placebo, late evening with nothing, and early morning with nothing. They found that the drug impaired lateral control but not speed control, and the effect was significant only with the higher, 10 mg, dose condition. In that condition there were marked impairments in lateral control with 10 mg diazepam, relative to all other condi-tions, which did not differ significantly from each other. In addition, the drop in performance between the control conditions and the 10 mg drive had "a corre-sponding drop in the subjective arousal." This led the authors to suggest that the drop in arousal is the mediating factor that causes the drop in performance after taking diazepam. However, this conclusion contradicts that of Rodrigo and Lusiardo (1988) in a later study (see below).

Barbiturates

Tedeschi, Bittencourt, Smith, and Richens (1983b) gave five healthy volun-teers a single oral dose of the barbiturate drug amylobarbitone sodium (200 mg) and placebo in a double blind randomized experiment and measured peak velocity of horizontal saccadic eye movements, saccadic duration and smooth pursuit velocity at intervals up to 6 hours after drug administration. The treatment produced a statistically significant decrease of both saccadic and smooth pursuit eye velocity with the maximum effect observed 2 hours after drug administration.

The effect on peak saccadic velocity was still statistically significant 6 hours after treatment. The maximum impairment in eye movement performance ranged between 25% and 29%. The results indicated that both saccadic and smooth pursuit systems were unable to generate the required eye velocity under the influence of a therapeutic dose of amylobarbitone sodium.

Only two other studies were found that evaluated the effects of barbiturates on performance without the interactions of alcohol. Both used different amounts of pentobarbitol, and the results of both suggest that barbiturates affect psychomotor functions in ways similar to that of alcohol.

In the first study Mintzer, Guarino, Kirk, et al. (1997) compared the effects of placebo, acute doses of the barbiturate pentobarbitol (150, 300, 600, and 750 mg/kg), and doses of ethanol (0.5, 1.0, and 2.0 g/kg) on psychomotor and cognitive performance. The subjects were 8 male volunteers, with a history of drug abuse, who were given all drug and alcohol levels (but not in combination). The researchers noted that both alcohol and pentobarbital produced similar dose-related effects on all psychomotor and cognitive measures, leading them to conclude that there is a "barbiturate-like rather than benzodiazepine-like profile of effects for ethanol".

Pickworth, Rohrer, and Fant (1997) evaluated the effects of two dose levels of marijuana, amphetamine, hydromorphine, pentobarbitol, and placebo on eight volunteers who received each drug dose on a separate day in a within-subjects design. They found that only alcohol and pentobarbitol impaired performance on reaction time to circular lights, digit symbol substitution test, serial math tasks, and card sorting. They also found that as the cognitive load of the card sorting task increased, ethanol and pentobarbitol impairments were detected at the lower doses.

CENTRAL NERVOUS SYSTEM STIMULANTS

Two types of stimulants are encountered in drivers: legal and illicit. The most common legal stimulant is caffeine (either in drinks or in pills), and the most common illicit stimulants are probably cocaine and amphetamine. Stimulants such as amphetamine causes changes in brain levels of dopamine, norepinephrine, and serotonin. These changes and interactions with other neurotransmitters may cause a wide array of impairments associated with euphoria, fatigue, confusion, and paranoia (Gjerde, Christophersen, and Morland, 1992).

Moskowitz and Burns (1981) observed that experiments examining whether central nervous system stimulants can antagonize the behavioral effects of alcohol have produced a considerable literature, with studies of caffeine-alcohol effects in humans indicating support for an antagonism of alcohol effects by caffeine for reaction time measures by ambiguity in results from other objective performance measures. They also concluded that evidence from animal studies which have examined wider dose ranges for both alcohol and caffeine indicates antagonism on

many measures of motor behavior with low to moderate caffeine and alcohol doses. On the other hand, they found that these earlier studies involving high caffeine doses appear to increase rather than offset the impairment due to alcohol.

Tedeschi, Bittencourt, Smith, and Richens (1983a) conducted two studies in which they administered either placebo or 15 mg d-amphetamine. In one study, with five subjects 22-32 years old, the drug was taken orally and in the other, with 6 subjects 20-35 years old, it was given intravenously. The authors measured effects on ocular behavior (peak saccadic velocity, saccadic duration, and saccadic reaction time). No differences were obtained between the placebo and amphetamine conditions with oral administration. However, with intravenous administration, there was no drop in peak velocity, and no increase in saccadic duration, but there was a drop in saccadic reaction time relative to drops obtained with placebo – especially at 30-50 minutes after drug administration. These results show the counteractive effects of amphetamine on fatigue-related eye movement effects – but only when administered intravenously.

Ward, Kelly, Foltin, and Fischman (1997) evaluated the effects of d-amphetamine on 6 healthy males living for 11 days in a residential laboratory. On each day they received either 0, 5, or 10 mg/kg d-amphetamine, a 6.5 hour work period and before a 6.5 hour recreation period. Amphetamine speeded up response on some tasks without any impairments in accuracy, and with no subjective effects. However, the researchers also found that amphetamine impaired digit symbol substitution test, and number recall in short-term memory. However, Pickworth, Rohrer, and Fant (1997) also failed to find any effects of amphetamine on reaction time to circular lights, digit symbol substitution test, serial math tasks, and card sorting.

Zancaner, Giorgetti, Dal Pozzo, Molinari, Snenghi, and Ferrara (1997) examined the blood or urine of 480 Italian drivers stopped by police for driving while impaired by alcohol or drugs, and correlated their findings with the results of clinical evaluations of impairment. Their results - not detailed in very exact terms - revealed that the following signs are indicative of drug impairments from stimulants:

- Mydriasis. Found in two thirds of those who had taken stimulants (amphetamines or cocaine).
- Conjunctival congestion. "Very high" in those who had taken stimulants (but also cannabis).
- Motor coordination. Not impaired by stimulants (but impaired - especially in the finger-to-nose test – by a "high percentage" of those taking opiates.
- High heart rate (>100). "Frequently" found in those who had taken stimulants and cannabinoids.

Compton, Shinar, and Shechtman (2000) also found that amphetamine was associated with increase in pulse rate and blood pressure but not in motor coordination, pupil reaction to light, or ocular convergence.

Mascord, Dean, Gibson, et al. (1997) compared the differential effects of five different stimulants "commonly used by truck drivers" on vital signs and a three-way divided attention task. The divided attention task consisted of a central tracking task, a peripheral visual discrimination task, and responding to a random visual "emergency" signal consisting of a red light display. The stimulants were all administered in a placebo-controlled design under laboratory conditions. They included caffeine (200 mg), ephedrine hydrochloride (60 mg), pseudoephedrine hydrochloride (60 mg), phentermine (30 mg) and diethylpropion (75 mg). For each drug, the performance and physiological measures were calculated by calculating a "drug-placebo" score. The results showed no significant effects on the divided attention task and no differences in systolic blood pressure or oral temperature. However, heart rate was lower after the intake of caffeine.

Ornstein, Iddon, Baldacchino, Sahakian, et al. (2000) studied groups of subjects whose primary drug of abuse was amphetamine or heroin, comparing them with age- and IQ-matched control subjects. The study consisted of a neuropsychological test battery which included both conventional tests and also computerized tests of recognition memory, spatial working memory, planning, sequence generation, visual discrimination learning, and attentional set-shifting. Many of these tests have previously been shown to be sensitive to cortical damage (including selective lesions of the temporal or frontal lobes) and to cognitive deficits in dementia, basal ganglia disease, and neuropsychiatric disorder. Qualitative differences, as well as some commonalities, were found in the profile of cognitive impairment between the two groups. The chronic amphetamine abusers were significantly impaired in performance on the extra-dimensional shift task (a core component of the Wisconsin Card Sort Test), whereas in contrast, the heroin abusers were impaired in learning the normally easier intra-dimensional shift component. Both groups were impaired in some of tests of spatial working memory. However, the amphetamine group, unlike the heroin group, were not deficient in an index of strategic performance on this test. The heroin group failed to show significant improvement between two blocks of a sequence generation task after training and additionally exhibited more perseverative behavior on this task. The two groups were profoundly, but equivalently, impaired on a test of pattern recognition memory sensitive to temporal lobe dysfunction. The authors concluded that these results indicate that chronic drug use may lead to distinct patterns of cognitive impairment that may be associated with dysfunction of different components of cortico-striatal circuitry.

In summary, it appears that while amphetamine is associated with some physiological reactions such as an increase in heart rate, mydriasis, and conjunctival congestion, it is usually not associated with easily observable behavioral impairments.

CANNABIS

Laboratory Studies

Moskowitz (1984) conducted multiple studies on the separate and joint effects of alcohol and different drugs on divided attention. He found two differences in attention that distinguished between alcohol and smoked marijuana (with 50, 100, and 200 μg/kg): (1) marijuana impaired peripheral detection of lights under both the focused and divided attention conditions, while alcohol did not, and (2) alcohol increased fixation durations in simulated driving while marijuana did not.

Perez-Reyes, Hicks, Bumberry, et al. (1988) gave six healthy moderate male users combinations of alcohol (placebo, 0.42 g/kg, and 0.85 g/kg) and marijuana cigarettes (with 0 or 2.4% THC). They measured accuracy and latency of performance in their "Simulator Evaluation of Drug Impairment" and found that marijuana increased alcohol-related impairments in a synergistic manner. They also found that marijuana accelerated heart rate.

Heishman, Stitzer, and Bigelow (1988) in a within-subject design, gave each of 6 male volunteers with mean age 26 years old one alcohol + marijuana dose on each of six counterbalanced sessions. Alcohol doses were .00, .07 or .13 BAC, and the marijuana cigarettes had 0, 1.3, or 2.7% THC. Marijuana produced only minimal decrement in the digit symbol substitution test, while alcohol impaired performance on all three cognitive measures used: simple reaction time to circular lights, digit symbol substitution test, and pursuit tracking on a choice reaction time. Heart rate increased in a dose-related manner in response to marijuana, but not in response to alcohol.

In a second study with marijuana only, Heishman, Stitzer, and Yingling (1989) gave 12 male users of marijuana cigarettes doses of 0, 1.3, or 2.7% THC, in a within-subject design, in 3 experimental sessions separated by 48 hours. As before, they found that subjects' feelings of a "high" and heart rate increased in a dose-related manner. More important, performance on short-term memory tasks as measured on forward and reverse attention span was impaired, and for the high dose condition, only performance was also impaired on the digit symbol substitution test. However, unlike the Moskowitz 1984 study, they did not find any impairments in a divided attention task.

Heishman, Huestis, Henningfield, and Cone (1990) evaluated marijuana effects on three regular users, using 0, 2.6%, and 5.1% THC, in a within-subject design. They obtained a subjective "high" for all subjects and a slight impairment in serial reaction time task (where subjects had to respond to a series of lights that appeared randomly, within a circle of 16 bulbs, and the score was the number of lights responded to in one minute). For two out of the three subjects, they also obtained impairments in digit recall and serial addition/subtraction. No significant impairments were found a day after smoking the marijuana. Performance in

a visual search task (two-letter cancellation task) and logical reasoning were not affected by marijuana in a consistent manner.

Chait and Perry (1994) studied the effects of marijuana (0 or 3.6% THC) alone or in combination with alcohol (.00 or .09 BAC), in a within-subject design, on 10 male and 4 female volunteers with a mean age of 25 years. They used both subjective measures of mood and objective measures of performance to observe both immediate effects and day-after effects. The visual analogue measures of feeling high and feeling drunk were very similar in magnitude for the marijuana alone and alcohol alone conditions, suggesting that they were able to match the level of perceived intoxication of the two drugs. Significant performance impairments due to marijuana were obtained only for time production (of 30, 60, and 120 seconds intervals). Alcohol resulted in overproduction (with subjects producing longer intervals), while marijuana caused underproduction. Performance on digit symbol substitution test, one-leg-stand, backward digit span, and free recall were impaired by alcohol only, and logical reasoning and divided attention were not impaired by either marijuana or alcohol. When impairment was demonstrated, it was only immediately following drug ingestion, with very little residual effects on the following day.

Heishman, Arasteh, and Stitzer (1997) evaluated the effects of placebo, three levels of alcohol (.025, .05, and .10 BAC), and three levels of marijuana (4, 8, or 16 puffs of marijuana cigarettes with 3.55% THC, yielding an average of 63, 150, and 188 ng/ml plasma THC) on five male, 18-26 years old volunteers. The order of the seven doses was random across subjects, and sessions were separated by one week. Subjective ratings on 12 perceived effects were made on visual analogue scales. Performance tests included simple reaction time, digit symbol substitution test for 90 seconds, number recognition test based on Sternberg test with variable memory set of seven digits, time estimation for durations of 5, 20, and 80 seconds, and immediate free recall for a list of 20 concrete nouns presented sequentially at the rate of 1 per 2 seconds. The results showed that heart rate increased in a dose-related manner for marijuana dosing but not for alcohol. Subjective ratings of impairment were very similar for the high doses of alcohol and marijuana, indicating that subjectively they were equivalent in their perceived strength. Both alcohol and marijuana impaired performance on digit symbol substitution test and immediate free recall. However, time perception and reaction time were not affected by either.

Berghaus, Kruger, Vollrath (1998) reviewed 66 studies that together provided 761 findings on different measures of perceptual-cognitive-motor performance. As expected, they found that the higher the concentration of THC, the greater the number of measures that were likely to indicate impairment: from 40% of the measures at 5 ng/ml plasma to a high of 70% of the measures at 55 ng/ml plasma. However, results with higher concentrations of THC were based on very few studies and are therefore less reliable.

Finally, in their analysis of the effects of different drugs on behavioral signs and symptoms recorded by drug recognition experts (DREs), Compton, Shinar, and Schechtman (2000) noted that marijuana caused a slowed pupil reaction to light, an increase in pupil size (both in the light and in the dark), an increase in pulse rate, and poor ocular convergence (of the two eyes toward a close object). Unlike alcohol, marijuana did not produce nystagmus or affect any of the common balance tests (one-leg-stand, finger-to-nose, and walk-and-turn).

Closed-Course and Driving Simulator Studies

Several studies have compared driving performance of cannabis-dosed drivers with that of drivers under the influence of either placebo or alcohol. These studies can be divided into two categories: driving in a simulator and driving an instrumented vehicle on the road.

Smiley et al. (1981) used an interactive simulator and found that in her high-dose condition (200 mcg/kg body weight THC), variability of lateral position in the lane, headway, and velocity increased significantly. Perceptual impairments were also manifested in an increase in reaction time to a subsidiary task, increase in missed turnoffs, and increase in crashes into obstacles on the road. However, a similar study reported by Stein, Allen, Cook, and Karl (1983) found far fewer effects of marijuana dosing. One possible explanation provided by Smiley to account for the difference between her findings and those of Stein's, is that Stein only measured performance over a 15-minute period whereas Smiley measured performance over a 45-minute period. It is then possible that the marijuana effects either increased over time, or that the ability of the drivers to continue to cope with these effects decreased over time. Unfortunately, a temporal analysis of performance over time to test this hypothesis was not conducted in either study.

The extensive studies by Robbe and O'Hanlon (1993), revealed that under the influence of marijuana, drivers are aware of their impairment, and when the experimental task allows it, they tend to actually decrease speed, avoid passing other cars, and reduce other risk taking behaviors. Given adequate warning, these drivers can also respond correctly and rapidly to dangerous situations. In contrast, the same studies showed that alcohol-impaired drivers are generally not aware of being impaired, and consequently they do not adjust their driving accordingly, and manifest more risk-taking behaviors.

In her recent review of the significant negative effects of marijuana, Smiley (1998) noted that performance in divided attention tasks is impaired. This is manifested in poorer performance on subsidiary tasks. The implication of this is that in situations where the drivers cannot adjust their speed to accommodate their slowed information processing, marijuana-impaired drivers may be less able to handle unexpected events.

Two recent studies were conducted on the effects of marijuana and alcohol, alone and in combination, on driving performance. The two studies that used

similar levels of alcohol and marijuana doses, but different measures of performance, reached somewhat different conclusions. The first of these studies, by Lamers and Ramaekers (1999) compared the effects of alcohol and THC alone and in combination, on subjectively-rated driving performance scores, relative to a placebo condition in a within-subject design. The 16 subjects (8 males and 8 females) had a mean age of 23, were all occasional users of alcohol and marijuana, and were treated on each session with either placebo and/or low levels of alcohol (.04 BAC) and/or low levels of THC (100 µgrams/kg THC). Although the levels were low, subjects generally correctly identified if they were truly dosed or not. Their task was to drive through city streets while responding to traffic controls, crossing intersections and making turns at intersections. Using driving instructors' performance scores, Lamers and Ramaekers found essentially no differences between the dosed and non-dosed conditions. However, they also found that drivers under the THC-only condition evaluated their performance as significantly worse than under the placebo, the alcohol and the alcohol+THC condition. Thus, the study confirmed the hypothesis that, unlike alcohol, marijuana actually enhances rather than mitigates the perception of impairment. The only negative behavioral effect of THC was a slight reduction in the frequency of intersections searched for cross traffic (based on the drivers' eye movement records). Although statistically significant, the drop was negligible: from a mean frequency of 85% of the intersections in the placebo condition, to a mean frequency of 82% in the combined alcohol+THC condition. Thus, in general, these results confirmed those of earlier studies with similar levels of THC.

In the second study, by Hindrik, Robbe, and O'Hanlon (1999), the participants' performance was evaluated in terms of subjective ratings as well as objective measures of lane tracking, maintaining a fixed speed (100 km/hr) and car following headway. The participants were eighteen 20-28 years old Dutch drivers who were moderate drinkers and marijuana smokers. The design was a double-blind crossover, in which each driver received all of the following six combinations of alcohol and marijuana: alcohol placebo+THC placebo, alcohol placebo+100 g/kg THC, alcohol placebo+200 g/kg THC, .04 BAC alcohol+THC placebo, .04 BAC alcohol+100 g/kg THC, and .04 BAC alcohol+200 g/kg THC. The results showed that THC impaired performance on both tasks, and that the effects were synergistic with alcohol. Thus, there was dose-dependent deterioration in lane tracking (both in standard deviation of lateral position and in total time out of lane), which was further exacerbated exponentially with alcohol. Finally, as observed before, the self rating of performance decreased with increasing levels of THC, but was not affected by the alcohol.

ANTIDEPRESSANTS

Hobi, Gastpar, Gastpar, et al. (1982) studied a group of twenty depressive patients during a 3-4 month course of antidepressant therapy, comparing them

with a healthy control group for subjective assessment of their depressive mood and performance as well as objective measurement of variables relating to driving behavior. The measurements were taken 2-4 weeks after a pre-treatment period (day 1) and after 2-3 months of further therapy (day 2). During therapy, all patients felt "less depressive" and "more capable" in subjective terms. All patient groups made learning progress in the objectively-measured variables (psychomotor co-ordination and attentiveness tests). By day 2, the patient groups had almost reached the performance level of the control group, providing they received antidepressant therapy (regardless of the action profile) which was suitable for the basic disorder and the symptoms, and therapy was successful in the opinion of the physician. The authors concluded that depressive patients, assuming suitable antidepressant treatment and good response, are more capable of driving while under maintenance therapy than driving while not under maintenance therapy.

Hindmarch, Subhan, and Stoker (1983) described the development of an objective measure of car driving performance, brake reaction time, and compared the effects of amitriptyline and zimeldine on this measure in a placebo-controlled, acute, single-dose, volunteer study. The effects of treatment on laboratory tests of critical flicker fusion threshold, choice reaction time and tracking accuracy and on self-assessments of sedation were also examined. At 2 hours post-treatment, amitriptyline produced a significant increase in brake reaction time when compared to both placebo and zimeldine. At 4 hours post-treatment, a significant reduction in "tracking accuracy" and a significant increase in choice reaction time was observed after treatment with amitriptyline, while no such effects were seen with zimeldine. Measures of critical flicker fusion threshold and self-ratings of sedation also revealed that amitriptyline produced a significant degree of sedation at 4 hours when compared to zimeldine and placebo. In contrast, zimeldine produced elevated critical flicker fusion threshold, but did not affect self-ratings of sedation.

Judd (1985) noted that, despite the extremely widespread use of antipsychotic medications, there is little evidence from the surveys conducted to date that this class of psychoactive medications is significantly implicated in vehicular crashes or deaths. He quoted epidemiologic evidence that, in five major surveys of vehicular fatalities in which drug and alcohol analyses were obtained, only two of over 800 victims studied involved detection of antipsychotic medications. He concluded that the acute administration of antipsychotics in normal individuals does induce sedation and performance decrements in visual-motor coordination and specific attention behaviors, which have a deleterious effect on driving behavior. On the other hand, he emphasized that antipsychotics are rarely used on an acute basis and tolerance to the sedation and decreased alertness does occur during chronic treatment. He noted that antipsychotic drugs have the capacity to potentiate the effects of alcohol, sedative hypnotics, narcotics and antihistamines, and therefore, combination of antipsychotics with these substances increases the impairment of driving behavior.

Judd also concluded that there is an indication that the less sedating piperazine phenothiazines and the butyrophenones may have little or no effect on psycho-motor performance, and antipsychotic drugs of these two subclasses may have a distinct advantage, at least in terms of driving performance, over the other more sedating drugs. Judd noted that antipsychotic drugs are almost never used for recreational or abuse purposes; therefore, the effect that antipsychotics may have on the driving behavior of those seriously disordered mentally ill patients who require continued maintenance on these medications should be of primary concern. Judd found good agreement in the literature suggesting that schizophrenic patients demonstrate improved psychomotor performance during chronic treatment with antipsychotic drugs. Thus, it is possible that despite the fact that antipsychotics have been shown, on an acute basis, to impair driving performance in normals, they may have a beneficial effect on driving behavior in schizophren-ics. Unfortunately, Judd found no study in the literature that focuses on the effect of long-term maintenance of antipsychotic drugs on driving performance of schizophrenic patients.

Linnoila and Seppala (1985) concluded that, although some impairment of skills due to antidepressants has been observed clinically, the impact of antide-pressants on traffic safety is at present [*circa* 1985] unknown. They observed that antidepressants (especially sedative antidepressants) and alcohol may have additive deleterious effects on skilled performance, and that combined effects are most prominent in the initial phase of treatment and diminish during prolonged treatment. They stated that the interaction with alcohol is mainly pharmacodynamic and indicated that major increases in the blood alcohol or antidepressant levels are uncommon in humans in social drinking situations, and minor changes are masked by individual pharmacokinetic variations. They concluded that an interaction between antidepressants and alcohol as well as the effect of untreated depression may be more important for traffic safety than drug effects alone.

Ramaekers, Swijgman, and O'Hanlon (1992) studied the acute and subchronic effects of moclobemide and mianserin on driving and psychometric performance, and compared these effects to those of placebo in a double-blind, crossover study involving 17 healthy volunteers. Mianserin, moclobemide and placebo were administered for 8 days. Subjects' performance was measured on days 1 and 8 of each treatment series; subjective sleep parameters, mood, and possible side-effects were recorded each treatment day on questionnaires or visual analog scales. Mianserin affected most of the performance measures, while moclobemide affected none; mianserin also impaired driving and tracking performance and decreased critical flicker fusion. While receiving mianserin, subjects reported depressed levels of alertness, calmness, and contentment; together with feelings of drowsiness and fatigue during the day. No statistical interactions between the factors "drugs" and (treatment) "days" were found, indicating that little pharmaco-logical tolerance developed over time during mianserin treatment. Mianserin's

sedative properties were held responsible for all performance and subjective effects of the drug. It was concluded that moclobemide 200 mg once a day has no important sedative properties.

Ramaekers, van Veggel, and O'Hanlon (1994) combined results from two separate studies that were used to compare the acute and subchronic effects of two monoamine oxidase-A (MAO-A) inhibitors, moclobemide and brofaromine, on actual driving performance and sleep. Both studies were conducted according to a double-blind, crossover design involving 18 patients receiving moclobemide and 16 patients receiving brofaromine. Patients were administered either moclobemide 200 mg b.i.d., mianserin 10 mg t.i.d., and placebo (study 1), or brofaromine 50 and 75 mg b.i.d., doxepin 25 mg t.i.d., and placebo (study 2) for 8 consecutive days[3]. A standardized driving test was conducted on day 1 and day 8 of treatment. Daily logs of estimated sleep duration and quality were obtained. Neither moclobemide nor brofaromine impaired driving performance. Some indication, although statistically not significant, was found that moclobemide improved driving performance on day 1. Brofaromine 75 mg significantly improved driving performance of day 8 of treatment.

The researchers found no significant difference between the effects of both drugs in a cross-study comparison. Moclobemide did not affect any sleep parameter, whereas brofaromine shortened sleep duration and decreased sleep quality. On day 1, mianserin and doxepin impaired driving. Impairment dissipated after 8 days of treatment with doxepin, but not during treatment with mianserin. Sleep duration was prolonged during treatment with both drugs, whereas sleep quality remained unaffected. It was concluded that both MAO-A inhibitors are safe drugs with respect to driving.

Ramaekers, Muntjewerff, and O'Hanlon (1995) examined the acute and subchronic effects of dothiepin 75-150 mg and fluoxetine 20 mg on critical flicker fusion frequency (CFF), sustained attention and actual driving performance, and compared the results with those of placebo in a double-blind, crossover study involving 18 healthy volunteers. Drugs and placebo were administered for 22 days in evening doses. Fluoxetine doses were constant but dothiepin doses increased on the evening of day 8. Performance was assessed on days 1, 8 and 22 of each treatment series. Subjective sleep parameters and possible side effects were recorded on visual analogue scales on alternate treatment days. The authors found that dothiepin reduced sustained attention on day 1 by 6.7% and CFF on day 22 by 1.1 Hz. Fluoxetine reduced sustained attention days 1, 8 and 22 of treatment by 7.4, 6.7 and 6.5% respectively. CFF decreased linearly over days during fluoxetine treatment and significantly differed from placebo on day 22 with 1.2 Hz. Neither drug significantly affected driving performance. While receiving dothiepin, subjects complained of drowsiness on days 1-3 of treatment and slept 43 minutes longer.

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[3] b.i.d is an abbreviation for "twice a day," and t.i.d. is an abbreviation for "three times a day."

van Laar, van Willigenburg, and Volkerts (1995) examined the acute and subchronic effects of two dosages of a new serotonergic antidepressant nefazodone, and those of the tricyclic imipramine in a double-blind, crossover, placebo-controlled study. Twenty-four healthy subjects from two age groups (12 adults and 12 elderly from both sexes) received the four treatments (nefazodone, 100 and 200 mg twice daily, imipramine 50 mg twice daily; and placebo) for 7 days with a 7-day washout period. Measurements were performed after the morning doses on day 1 and day 7. These included a standard over-the-road highway driving test, a psychomotor test battery, and sleep latency tests. Blood samples were taken on both days and analyzed to determine concentrations of parent drugs and their major metabolites. It was found that the reference drug, imipramine, had a detrimental effect after a single dose on lateral position control in the driving test, primarily in the adult group, that diminished after repeated dosing. Minor impairment on psychomotor test performance was found on both days. On the other hand, a single administration of both doses of nefazodone did not impair highway driving performance (even showed some improvement) and had no or only minor effects on psychomotor performance. After repeated dosing, nefazodone (200 mg twice daily, but not the 100-mg dose) produced slight impairment of lateral position control; dose-related impairment of cognitive and memory functions also was found. The effects of nefazodone were generally in the same direction in both age groups. Significant correlations were found between steady-state concentrations of nefazodone in plasma (200-mg, twice-daily condition) as well as imipramine, and reaction time changes in a memory scanning task. Neither drug appeared to induce daytime sleepiness as measured by the sleep latency tests.

Ramaekers, Annseau, Muntjewerff, et al. (1997). Studied parallel groups of depressed (DSM III-R) outpatients who received moclobemide (n=22) and fluoxetine (Prozac) (n=19), double-blind, for 6 weeks. Respective starting doses were 150 mg twice a day and 20 mg q.a.m. (every morning). These could be doubled afer 3 weeks for greater efficacy. Chronic users of benzodiazepine anxiolytics continued taking them as co-medication. Therapeutic and side effects were assessed using conventional rating scales. Actual driving performance was assessed during the week before therapy and at 1, 3 and 6 weeks thereafter using a standardized test that measures standard deviation of lateral position (SDLP). Similar remissions in depressive symptoms and side effects occurred in both groups. Patients drove with normal and reliable (r=0.87) SDLPs before treatments. Most continued to do so but a few drove with progressively rising SDLPs and the overall trends were significant in both groups (p<0.03). A post-hoc multiple regression analysis was applied for identifying factors that correlated with SDLP in separate tests after the beginning of therapy. At 3 and 6 weeks there were significant (p<0.03) relationships involving the same factor; patients who drove with progressively higher SDLPs appeared to be those using

benzodiazepines that are metabolized by a P450 isozyme subject to inhibition by their particular antidepressant.

O'Hanlon, Robbe, Vermeeren, et al. (1998) studied the effects of venlafaxine, an antidepressant acting by selective serotonin and norepinephrine re-uptake inhibition with a potency ration of 51, in a standardized, actual driving test, a battery of psychomotor tests (critical flicker fusion frequency, critical tracking, divided attention), and a 45-minute vigilance test. Thirty-seven healthy volunteers, 22 of whom completed the study, received venlafaxine in fixed (37.5 mg twice a day) and incremental (37.5-75.0 mg twice a day) doses as well as mianserin (10-20 mg three times a day) and placebo according to a 4-period (15 days each), double-blind, crossover design. Testing occurred on days 1 and 7 and after dose increments, on days 8 and 15. The results indicated that venlafaxine does not generally affect driving ability and should be safe for use by patients who drive.

ANTIHISTAMINES

Histamine mediates numerous processes in nearly all organs and tissues. Too much histamine can create allergic reactions and other physical problems, and antihistamines restrict the release of histamine to the cells. Histamines are categorized according to the three types of cell-surface receptors (called H1, H2, and H3 receptors) the histamine bind to. The most pertinent of these to this review are the H1 receptors, and H1 antihistamines restrict the release of histamines to the H1 receptors. Older H1 antihistamines (1st generation H1 antihistamines) have been found to cause side effects such as drowsiness, which are greatly reduced by the newer, 2nd generation H1 antihistamines.

Betts, Markman, Debenham, et al. (1984) conducted a double-blind, placebo, controlled experiment measuring the effects of 1st generation antihistamine triprolidine and the and the 2nd generation antihistamine terfenadine on actual driving performance in a group of experienced women drivers. They found that triprolidine greatly impaired driving behavior, whereas terfenadine did not. Triprolidine also impaired subjective and objective measures of mood and arousal, and despite an awareness that their driving was impaired while they were taking this agent, subjects could not correct their performance. The researchers concluded that this study suggests that drivers who need antihistamine drugs should avoid those that act centrally.

Starmer (1985) reviewed available evidence that antihistamine-induced impairment of human psychomotor performance constitutes a traffic hazard. He noted that there were two distinct classes of histamine antagonists, which act at different receptors (H1 and H2), and that they should be considered separately. H1 antagonists are freely available to the public and are widely consumed. He also noted that they are a rather heterogenous group of drugs which share the common property of antagonizing some of the effect of histamine. Starmer

indicated that other effects, particularly sedation, are prominent with many of the older members of the H1 group, and these drugs can be shown to impair performance in laboratory tasks and to interact additively with alcohol and other central nervous system depressant drugs. Despite this potential for impairment of driving ability, Starmer observed that they are seldom suggested as causative factors in traffic crashes. He pointed out that a number of new histamine H1 antagonists have been developed recently which only gain limited access to the central nervous system and appear to be less likely to cause impairment of performance skills. Histamine H2 antagonists have a much more restricted and closely supervised use in medicine, and of the two agents currently available (cimetidine and ranitidine), only cimetidine appears to pose traffic safety problems, largely because of its ability to interfere with the metabolism of other drugs which depress the central nervous system. He recommended appropriate prescribing to eliminate this problem. Starmer concluded that, with both classes of histamine antagonist, it is now possible for the prescriber to select from the available drugs one with a minimal potential for disrupting driving ability.

In a later review (limited to H1-receptor antagonists), Simons (1994) also observed that 1st generation histamine H1-receptor antagonists frequently cause drowsiness or other CNS adverse effects, but that 2nd generation H1-antagonists have a relative lack of such effects. He noted that even the 2nd generation drugs can create some risk and recommended that "the magnitude of the beneficial effects of each H1-antagonist should be related to the magnitude of the unwanted effects, especially in the CNS and cardiovascular system, and a benefit-risk ratio or therapeutic index should be developed for each medication in this class."

Moskowitz and Wilkinson (2003) have just completed a review of the scientific literature on the effects of H1-antagonist antihistamines on driving and driving-related performance. Studies relating to five 1st generation drugs (chlorpheniramine, clemastine, diphenhydramine, hydroxyzine, and triprolidine) and five 2nd generation drugs (astemizole, cetirizine, fexofenadine, loratadine, and terfenadine) were included in the review. The authors found that 88% of the studies of 1st generation antihistamines found some impairment in driving related skills, but that only 22% of the 2nd generation antihistamines found such impairments. However, the percent of drugs within each generation and the percent of studies showing impairment varied widely among specific drugs within each generation.

Performance of driving tasks was impaired in 13% of the 32 studies that examined driving behavior. When the tasks are limited to actual driving, only 10% of the 20 studies showed impairment. Analysis of studies focusing on cognitive and psychomotor skills yielded similarly low rates. Most 1st generation drugs resulted in a feeling of sedation and a change in the EEG, whereas the overwhelming majority of the 2nd generation antihistamines did not result in such feelings or physiological changes. Consistent with these findings, most studies of 1st generation drugs showed impairments on visual functioning, divided attention,

vigilance, and tracking, while studies of the studies of 2nd generation antihistamines rarely showed any impairments on any of the tasks studied. Furthermore, the authors note that in many cases where impairment was shown, the dose levels greatly exceeded the recommended therapeutic levels. In conclusion, the authors note that "it would appear that proper selection of a 2nd generation antihistamine would produce little skills performance impairment. Therefore, one would not anticipate a significant effect on traffic collisions." (p. 20).

Selected experimental studies of both H1- and H2- receptor antagonist drugs published since the late 1980s are summarized in the remainder of this section. Some of the studies reviewed by Moskowitz and Wilkinson are included.

O'Hanlon (1988) reported that the results of two placebo-controlled driving performance studies confirmed prior laboratory data showing that terfenadine does not adversely affect the driving performance of users. The amplitude of vehicle weaving calculated for drivers who received this agent did not differ from control values. Neither terfenadine nor loratadine, another nonsedating antihistamine, potentiated the adverse effects of alcohol on driving performance.

Ramaekers, Uiterwijk, and O'Hanlon (1992) report the results of a study in which 16 healthy male and female volunteers took part in a 6-way, double-blind crossover trial to compare the effects of single doses of the 2nd generation H1-receptor antagonists cetirizine (10 mg) and loratadine (10 mg), with placebo, with and without alcohol (0.72 g/kg, lean body mass). Performance was measured in two repetitions of a psychometric test battery, and a standard, over-the-road driving test. EEG was also measured during driving. Alcohol significantly affected almost every performance measure and altered the EEG energy spectrum during driving while the blood concentrations declined from 0.37 to 0.20 mg/ml. The effects of cetirizine on driving performance resembled those of alcohol. It caused the subjects to operate with significantly greater variability in speed and lateral position ("weaving" motion). The effects of alcohol and cetirizine appeared to be additive. Certain cetirizine-placebo differences in subjective feelings and test battery performance were also significant. Loratadine had no significant effect on any performance parameter. The authors concluded that cetirizine, but not loratadine, generally caused mild impairment of performance after a single 10 mg dose.

Ramaekers and O'Hanlon (1994) conducted another study of antihistamines following a nine-way observer- and subject-blind, crossover design. Its purpose was to compare the single-dose effects of the following drugs on driving performance acrivastine (8, 16 and 24 mg); the combination of acrivastine (8mg) with pseudoephedrine (60mg); terfenadine (60, 120 and 180 mg); diphenhydramine-HCI (50mg); and placebo. The subjects were 18 healthy female volunteers. Drug effects were assessed in two repetitions of two driving tests (highway driving and car-following) after each treatment. The study indicated that the normal therapeutic dose of acrivastine (8 mg) had little effect on driving performance, and virtually none when that dose was given in combination with pseudoephedrine (60

mg). Higher doses of acrivastine severely impaired driving performance. Terfenadine had no significant effect on driving performance after any dose while diphenhydramine strongly impaired every important driving parameter.

Vuurman, Uiterwijk, Rosenzweig, and O'Hanlon (1994) compared the acute effect of doses of mizolastine 5, 10, 20 and 40 mg, an active control (clemastine 2mg) and placebo on actual car driving and psychomotor performance. Twenty four healthy volunteers were treated according to a doubt-blind, 6-way crossover design. In the driving test, lasting about 1 hour, lateral position control and speed were continuously measured; the psychomotor test battery, lasting 50 minutes, comprised critical flicker fusion frequency, critical instability tracking, divided attention, memory search and choice reaction time, and vigilance studies; and mood changes and possible adverse effects were rated on visual analogue scales. The results showed a dose-response relationship. Mizolastine 40 and 20 mg impaired driving and psychomotor performance. The effect of mizolastine 40 mg on driving was strongly correlated with that of clemastine (r=0.78) and was comparable to the effect of a blood ethanol level of 0.8 mg/ml. Mizolastine 5 mg and 10 mg did not have a significant effect on driving performance and psychomotor tests. It was concluded that at a 10 mg dose of mizolastine, the therapeutic dose, it could be considered a safe antihistamine, although individual adverse reactions cannot be completely ruled out.

O'Hanlon and Ramaekers (1995) reviewed the major results of eight double-blind placebo-controlled, volunteer studies undertaken by three independent institutions for showing the effects on actual driving performance of "sedating" and "nonsedating" antihistamines (respectively, triprolidine, diphenhydramine, clemastine and terfenadine; and loratadine, cetirizine, acrivastine, mizolastine, and ebastine). A common, standardized test was used that measures driving impairment from vehicular "weaving" [i.e., standard deviation of lateral position (SDLP)]. Logical relationships were found between impairment and dose, time after dosing, and repeated doses over 4-5 days. The newer drugs were generally less impairing, but differences existed among their effects, and none was unimpairing at doses 1-2 times the currently recommended levels. One or possibly two of the newer drugs possessed both performance-enhancing and impairing properties, depending on dose, suggesting two mechanisms of action.

Vermeeren and O'Hanlon (1998) studied the effects of fexofenadine on performance for the purpose of determining its safety of use by patients who engage in potentially dangerous activities, especially car driving. (Fexofenadine is the hydrochloride salt of terfenadine's active metabolite.) Fexofenadine was administered in daily doses of 120 or 240 mg. each in single and divided units given over 5 days. Two milligrams of clemastine given twice daily and placebo were given in similar series. Twenty-four healthy volunteers (12 men, 12 women; age range 21 to 45 years) participated in a double-blind six-way crossover study. Psychomotor tests (critical tracking, choice reaction time, and sustained attention) and a standardized actual driving test were undertaken between 1.5 to 4 hours

after administration of the morning dose on days 1, 4, and 5 of each series. On day 5, subjects received a moderate alcohol dose before testing. Fexofenadine did not impair driving performance. On the contrary, driving performance was consistently better during twice daily treatment with 120 mg fexofenadine than during treatment with placebo, significantly so on day 4. Both of the 240 mg/day regimens significantly attenuated alcohol's adverse effect on driving on day 5. Effects in psychomotor tests were not significant, with the exception of the critical tracking test in which the first single doses of fexofenadine, 120 and 240 mg. had significantly impairing effects. It was concluded that fexofenadine has no effect on performance after being taken in the recommended dosage of 60 mg twice daily.

Finally, Weiler et al. (2000) compared the effects of fexofenadine, diphenhydramine, alcohol, and placebo on driving performance. They used a randomized, double-blind, double-dummy, four-treatment, four-period crossover trial conducted in the Iowa Driving Simulator. The trial involved 40 licensed drivers with seasonal allergic rhinitis who were 25 to 44 years of age. One dose of fexofenadine (60 mg), diphenhydramine (50 mg), alcohol (approximately .10 blood alcohol concentration), or placebo, was given at weekly intervals before participants drove for 1 hour in the Iowa Driving Simulator. The main objective was to measure coherence, defined as "a continuous measure of participants' ability to match the varying speed of a vehicle that they were following." The study also measured subject drowsiness and other driving variables, including lane keeping and response to a vehicle that unexpectedly blocked the lane ahead. Participants had significantly better coherence after taking alcohol or fexofenadine than after taking diphenhydramine. Lane keeping (steering instability and crossing the center line) was impaired after alcohol and diphenhydramine use compared with fexofenadine use. Mean response time to the blocking vehicle was slowest after alcohol use (2.21 seconds) compared with fexofenadine use (1.95 seconds). Self-reported drowsiness did not predict lack of coherence and was weakly associated with minimum following distance, steering instability, and left-lane excursion. The authors concluded that the participants had similar performance when treated with fexofenadine or placebo, and that driving performance was poorest after taking diphenhydramine. The authors also found that drowsiness ratings were not a good predictor of impairment, "suggesting that drivers cannot use drowsiness to indicate when they should not drive."

OTHER DRUGS

In a study by Klebel, Saam, and Hoffman (1985), 21 hypertensive patients received (after a one-week placebo period) a 4-week treatment with a once daily dose of 300 mg of the *antihypertensive* celiprolol hydrochloride (Selectol). Twenty-one normotensive subjects receiving placebo during the whole trial period and 20 normotensives receiving no treatment at all served as comparative groups.

Prior to the treatment, the hypertensive subjects showed a marked lack in acquisition and reproduction of complex visual information, and their subjective emotional condition was more negative than that of the healthy subjects. A one-week placebo treatment had no influence on the parameters under test. One single dose of celiprolol had no influence on the specific capacity of driving a motor vehicle and on the emotional condition. Long-term medication of celiprolol did not impair the driving ability. The subjective emotional condition improved as desired. Another study (reviewed on page 31) also found that mepindolol sulphate, a beta blocker without sedating properties, did not impair driving or driving-related performance (Willumeit, Ott, Neubert et al., 1984).

Betts, Harris, and Gadd (1991) examined the effects of the *antivertigo* drug betahistine on driving. In the study, 72 mg were taken three times daily, prochlorperazine 5 mg were taken three times daily, and placebo was taken for 3 days before testing. Then, the subjects were compared on two actual driving tasks (weaving and gap estimation) and two psychomotor tasks (reaction time and kinetic visual acuity) in normal subjects.   The results showed that the psychomotor effects of betahistine could not be distinguished from those of placebo and that prochlorperazine impaired driving performance causing increased carelessness and slowing on the weaving test. Also, there was little subjective appreciation of impairment during taking prochlorperazine.

Wylie, Thompson, and Wildgust (1993) noted that patients who are prescribed psychotropic medication may be expected to have some impairment in general attention and concentration and in measures of psychological and motor performance. These impairments may be due to the illness itself, the medication or the combination of both. In this study, 22 patients who were receiving injections of *neuroleptics* for chronic schizophrenia were compared with 16 control subjects in their performance on simulated driving tests. The researchers found a significant decrement in driving performance in the index group compared with a normal control group.

Vuurman, Muntjewerff, Uiterwijk, et al. (1996) performed studies to determine whether mefloquine, a quinoline *anti-malarial* drug, affects psychomotor and actual driving performance when given in a prophylactic regimen, alone or in combination with alcohol. Forty male and female volunteers were randomly assigned in equal numbers to two groups, and were treated double-blind for one month with mefloquine and placebo. The medication was taken in a 250 mg dose on the evenings of days 1, 2, 3, 8, 15, 22 and 29. Testing was done on days 4, 23 and 30, the latter after repeated doses of alcohol sufficient to sustain a blood concentration of about .35 mg/ml. Two real driving tests were used to measure prolonged (1 hour) road tracking and car following performance; critical flicker fusion frequency, critical instability tracking, and body sway were also measured in the laboratory. Mefloquine caused no significant impairment in any test at any time relative to placebo. It significantly improved road tracking performance on day 4. A significant interaction between prior treatment and alcohol was found in

the body sway test, as the alcohol-induced change was less after mefloquine than placebo. The sensitivity of the driving test and the critical flicker fusion frequency test were shown by the significant overall effect of alcohol which did not discriminate between the two prior treatments.

Ellingrod, Perry, Yates, et al. (1997) examined the driving effect of *anabolic steroids* in the form of physiologic (100 mg/wk) and supraphysiologic (250 and 500 mg/wk) doses of testosterone cypionate (TC). The Iowa Driver Simulator was used in the study. Six normal subject volunteers were studied off TC and on TC once steady-state concentrations were achieved after at lease three weeks of dosing. Despite the administration of supraphysiologic testosterone doses, an increase in aggressive driving behavior was not detected. Likewise, corresponding psychometric testing was unable to detect any change in aggression in the test subjects. Although aggressive driving behavior may be increased by testosterone administration, the drug itself may not be responsible for these effects. Supraphysiologic doses greater than 500 mg/wk and a semi-controlled research environment may be necessary to produce this effect, since case reports of anabolic steroids abuse causing altered driving behavior may be multifactorial in nature.

Grant, Murdoch, Millar, and Kenny (2000) studied psychomotor performance in 10 healthy volunteers during recovery after a target-controlled infusion of *propofol* anaesthesia. Choice reaction time, dual task tracking with secondary reaction time and a within-list recognition task were assessed at target blood propofol concentrations of 0.8, 0.4 and 0.2 mμg/ml. Performance was impaired most at the highest blood propofol concentration (choice reaction time increased by a mean of 247 ms and secondary reaction time by a mean of 178 ms). Choice reaction time and dual task tracking with secondary reaction time were the most sensitive and reliable methods of assessment [significant difference from baseline ($p<.05$) at a propofol concentration of 0.2 mμg/ml with choice and secondary reaction time testing]. Within-list recognition assessment of memory was not sufficiently sensitive at very low propofol concentrations. The impairment in choice and secondary reaction time with a blood propofol concentration of 0.2 mμg/ml was less than that observed with a blood alcohol concentration of .05 and no greater than that observed with a blood alcohol concentration of .02 in a previous study involving healthy volunteers.

SUMMARY AND CONCLUSIONS

Selected literature on the effects of a wide range of drugs on performance of driving-related tasks and performance of actual driving tasks was reviewed. Classes of drugs considered were:

■ narcotics,
■ central nervous system (CNS) depressants,

- ■ CNS stimulants,
- ■ cannabis,
- ■ antidepressants,
- ■ antihistamines, and
- ■ other drugs that have been investigated in a few individual studies.

The amount of research in these classes varied widely, with the most attention given to CNS depressants and the least given to narcotics. We found essentially no experimental research on some other classes of drugs not listed above, for example, hallucinogens and inhalants.

With respect to *narcotics*, one laboratory study of a synthetic opioid (fentanyl) showed impairment on a tracometer task, another finding no difference in the performance of chronic users of methadone and non-users in driving-related tasks, and a third finding that the only significant effect of codeine on signs and symptoms in NHTSA 's DEC program was a reduction in pupil size. However, a 1974 simulator study found that acute codeine use resulted in more crashes, more instances of leaving the road, and more ignoring of instructions. Lastly, a simulator study of persons using narcotics in the treatment of chronic non-malignant pain found no significant impairment. These sparse results suggest that acute use of narcotics can definitely impair driving performance, but that chronic therapeutic use need not cause impairment.

For *CNS depressants*, two sub-classes, benzodiazepines and barbiturates, have received the bulk of the attention in the literature. Of these, the *benzodiazepines* have generated most of the studies. The variety of benzodiazepines is wide, with most of them falling into two categories, those with effects having a short half-life (peaking at two to three hours) and those with effects having a long half-life (lasting nine or more hours). Tested benzodiazepines classified as short half-life included flurazepam, temazepam, and triazolam. Tested long half-life benzodiazepines included alprazolam, diazepam, flunitrazepam, lorazepam, and nitrazepam.

Nearly three-fourths of the experiments on benzodiazepines of all types found impairments of one or more tasks or functions. Interestingly, a larger percentage of driving experiments than laboratory experiments indicated significant impairment (79% vs. 70%, respectively). The research indicates that the impairing effects of benzodiazepines can vary wide for different members of the drug class: for example, diazepam consistently impaired performance in two-thirds of the pertinent experiments, while clobazam caused impairment in only one very high-dose experiment. Not surprisingly, the research indicates a clear dose-response relationship for benzodiazepines – 87% of experiments using high dosages found impairment. A few experiments tested the effect of chronic and sub-chronic use of benzodiazepines, with the results suggesting impairments in some tasks after a week or so of usage. Residual ("hangover") effects of several benzodiazepines used as hypnotics were also found. In sum, the research indicates that most

benzodiazepines can cause significant impairment of driving and driving-related tasks, especially at high dosages. However, it has been argued that therapeutic dosages create impairments that may be less hazardous to driving than the illnesses they are treating.

Only three studies were found dealing with *barbiturates* alone, all indicating impairment of one or more tasks over a range of dosages. The tasks included those that were both cognitive and psychomotor in nature, including eye movements, digit symbol substitution, and card sorting. In one study, it was concluded that pentobarbital produced dose-related effects similar to those of alcohol on all psychomotor and cognitive measures.

While the research on the effects of CNS depressants indicate a high potential for impairment of driving and driving-related tasks, the very sparse experimental literature indicates that the opposite is true for *CNS stimulants*. Laboratory tests of acute effects showed either no impairment or improvement on various psycho-motor and cognitive tasks, but a test of chronic users indicated impairment of card sorting and memory tasks.

Experimental research on the effects of *cannabis* have produced mixed results, indicating that any effects (slightly over half of the experiments we examined showed impairment) dissipate quickly after one hour, so that a day after ingestion they are no longer significant. Furthermore, while drivers feel high, they actually tend to compensate for their feelings. Of the behavioral measures studied, marijuana seems to effect the encoding of information and its short-term storage. It has been found that marijuana impairs digit span (forward and backward) and time estimation. While alcohol causes an underestimate of time, marijuana causes an overestimate of time, and consequently an under-production in time-production tasks. Impairments in tracking and reaction time have also been noted, but in a much less consistent manner than with alcohol impairment. Experiments in actual driving tasks indicated impairment in a range of such tasks, including maintaining lateral position, headway, and speed: negotiating turn-offs; avoiding crashes; and performing secondary tasks. [Ward and Dye (1999) present an excellent summary of the effects of cannabis on various aspects of driving and driving-related performance.]

A considerable body of literature on the behavioral effects of *antihistamines* has been created in recent years. So-called H1 antihistamines (which restrict the release of histamines to cells) have been the subject of nearly all of this research. Older H1 antihistamines (1st generation H1 antihistamines) have been found to cause side effects such as drowsiness, which are greatly reduced by the newer, 2nd generation H1 antihistamines.

The recent review by Moskowitz and Wilkinson (2001) examined 130 articles on the effects of five "key" 1st generation and five key 2nd generation H1 antihistamines on driving and driving-related performance. They found that 88% of the studies of 1st generation antihistamines found some impairment in driving related skills, but that only 22% of the studies of 2nd generation antihistamines found such

impairments. Performance of driving tasks was impaired in 13% of the 32 studies that examined driving behavior. Studies of cognitive and psychomotor skills yielded similarly low percentages. Most 1st generation drugs created a feeling of sedation and caused impairments of various psychomotor tasks, but few 2nd generation antihistamines resulted in such feelings or impairments.   Most important, the dose levels causing impairment very often greatly exceeded the recommended therapeutic dosages. Our own examinations of a number of laboratory and driving experiments involving H1 antihistamines produced findings that were consistent to those of Moskowitz and Wilkinson. We found no studies of the effects of H2 or H3 antihistamines on driving and driving-related performance.

Several *anti-depressant* drugs have been tested in a few studies to determine their effects on driving and driving-related tasks. These drugs include: amitript-yline, brofaromine, doxepin, fluoxetine, mianserin, moclobemide, venlafaxine, and zimeldine. Of these, only amitriptyline, doxepin, and mianserin have been found to impair driving. It is believed that such impairment is due primarily to the sedative effects of these three drugs.

Finally, the experiments dealing with six *other drugs* not in any of the above categories (an anti-hypertensive drug, an anti-vertigo drug, an injected neuroleptic drug for treating schizophrenia, an anti-malarial drug, an anabolic steroid, and propofol anaesthesia) found impairment for only two of the drugs. Schizophren-ics undergoing treatment involving chronic use of the neuroleptic were more impaired than a group of normals not using a neuroleptic, but it could not be said whether the drug or the illness or both caused the impairment. And the impair-ment by propofol was during recovery after anaesthesia when driving would not be likely.

It is difficult to generalize further about such a diverse group of drugs, but a few broad conclusions seem warranted. With respect to *acute effects*, it appears that the following drug classes have a high potential for significant impairment of driving and driving-related performance:

- narcotics,
- long-life benzodiazepines in therapeutic doses,
- short-life benzodiazepines in high doses,
- barbiturates,
- 1st generation H1 antihistamines, and
- certain anti-depressants (amitriptyline, doxepin, and mianserin).

Drugs classes with a relatively low potential for significant impairment after acute usage are CNS stimulants (which actually may improve performance in some instances), 2nd generation H1 antihistamines, and most other anti-depres-sants. In addition, the literature suggests that acute use of cannabis has a moder-ate potential for impairment.

Very few studies examined the chronic and sub-chronic use of the above classes of drugs, and most of those that did suggest little effect on driving and driving-related performance. Interestingly, one study finding a clear effect (on card sorting and memory) involved a stimulant, d-amphetamine. Also, another study found that the anti-depressant mianserin impaired actual performance after eight days of use.

All-in-all, the literature supports the common-sense notion that drugs with a strong sedative action taken in the highest doses have the highest potential for significant impairment, while others have the lowest potential. Other meta-generalizations about which tasks and functions are impaired by which doses of which drugs cannot be made on the basis of the literature we examined.

5 - EPIDEMIOLOGIC RESEARCH

INTRODUCTION

The major focus of this chapter is drug effects on overall crash prevalence and risk as determined from epidemiologic studies. Major categories of research of interest here are:

- research based on traffic crash data as taken from police accident reports;
- research based on data on drivers who have been arrested for drugged driving, drunk driving, or other traffic offenses;
- research based on data collected by medical examiners or coroners in the course of examinations of drivers who have been killed in traffic crashes;
- research based on data collected by trauma units and hospitals on drivers who have been brought there following a traffic crash;
- research based on drivers tested at the roadside; and
- self-reported data flowing from surveys of drivers.

These categories are addressed in four sections of this chapter, as follows:

- Drugs in crash-involved drivers;
- Drugs in non-crashed, on-the-road drivers;
- Drug-crash risk; and
- Drugs in drivers stopped or arrested for traffic violations.

Within each section, there are two sub-sections, the first dealing with research conducted in North America (the United States and Canada), and the second with research conducted elsewhere (foreign studies).

DRUGS IN CRASH-INVOLVED DRIVERS

North American Studies.

Several studies have examined the presence of drugs in crash-involved drivers in the United States. The largest of those concerned with *fatally-injured drivers* was the NHTSA-sponsored study of 1,882 operators of passenger cars, motorcycles, and trucks who were involved in fatal crashes in three states and selected counties in four other states during 14 months in 1990-1991 (Terhune, Ippolito, Hendricks et al., 1992). Researchers in that study collected blood specimens from a sample of all drivers who had died within four hours after the crash. Samples were analyzed qualitatively for alcohol and 43 other drugs, many which were no

longer in use at the time of the study. Alcohol was the most prevalent drug, and was found in 51.5% of the crashes; other drugs were found in 17.8% of the crashes. The study found cannabinoids present in 6.7% of the drivers, cocaine in 5.3%, benzodiazepine in 2.9% and amphetamines in 1.9%. All other drugs combined were found in less than 5.0% of the drivers. Drugs were found in conjunction with alcohol in 11.4% of the cases.

Studies of fatally-injured drivers in more limited geographical areas have reported similar findings. For example, Williams, Peat, Couch, et al. (1985) found one or more drugs in 81% of 440 male drivers, aged 15-34, killed in motor vehicle crashes in California, and two or more drugs were detected in 43%. Marijuana was detected in 37% of the drivers, and cocaine in 11%. Each of 24 other drugs was detected in fewer than 5%. Except for alcohol, drugs were infrequently found alone; typically, they were found in combination with high blood alcohol concentrations.

In another California study, Budd, Muto, and Wong (1989) conducted a study in which the blood and urine of 594 fatally injured drivers from Los Angeles County were tested for drug and alcohol levels over two different time periods from 1985 to 1988. The first part of this study (November 1985 - April 1986) found that 12% of 102 drivers tested were positive for "drugs of abuse." In a follow-up study covering a longer time period (May 1987 - May 1988), 15% of 492 drivers were positive for such drugs, 8% for marijuana and 7% for cocaine. Root (1989) found "drugs of abuse" (unspecified) in 13% of 796 fatally injured California drivers tested during the 1985-1987 period. Caplan, Levine, and Goldberger (1989) reported marijuana present in 7% of the 269 fatally injured drivers tested in Maryland over an unspecified 10-month period, and cocaine in 8%. Caplan and associates also found none of the drivers positive for amphet-amines, and 3% positive for phencyclidine (PCP).

Rivara, Mueller, Fligner, et al. (1989) found that about 10% of 160 fatally injured *occupants* in King County, Washington (Seattle) in 1986 were positive for THC, and that 2% were positive for cocaine. The paper did not provide any breakdowns by type of occupant (driver or passenger). In a study in nearby British Columbia, Jeffrey, Leslie, and Mercer (1995) reported the results of chemical analyses of the blood of 222 fatally injured drivers in British Columbia, Canada in 1991. This paper also reported the level of the drug for each drug-positive subject. Percentages of cases and mean level for each drug were: THC / THCCOOH (13%, 14.7 ng/ml); cocaine (4%, 131 ng/ml for six cases positive for cocaine + metabolite); and benzodiazepines (5%, 405 ng/ml for 10 subjects with diazepine, 1,480 NG/ml for one subject with nordiazepine). Six cases (3%) contained other drugs.

Fortenberry, Brown, and Shevlin (1986) reported the results of another study of drug presence in fatally injured occupants (this time in Alabama), indicating that almost 17% tested positively for marijuana. Sixty-four percent of the marijuana-positive victims were drivers. More than 5% of fatalities had some

level of drugs (either illicit or prescription) in their blood stream. The drugs that were found and their percent of all drivers were diazepam (2.1%), methaqualone (2.2%), phenobarbital (1.0%), and propoxyphene (0.3%). (Methaqualone is a depressant no longer legal in the U. S., and propoxyphene is a narcotic analgesic.) A statistically significant association (p=0.05) was found between diazepam and low BAC.

Marzuk, Tardiff, Leon et al. (1990) found cocaine in about 14.1% of the 643 motor vehicle occupants killed in traffic crashes in New York City during the period 1984-1987. Cocaine was the only drug screened for, and its presence was determined primarily from chemical tests for the cocaine metabolite benzoy-lecgonine. There was no statistical difference in this percentage with respect to ridership status (driver or passenger).

The results of tests of blood and/or urine from 347 fatally injured drivers in Washington State were reported by Logan and Schwilke (1996). Drugs most commonly encountered were marijuana (11%), cocaine (3%), and amphetamines (2%), together with a variety of depressant prescription medications including narcotics, benzodiazepines, barbiturates, and anti-depressants. Trends noted included an association of depressant use with higher BACs, while marijuana use was associated with lower BACs. Marijuana use was noted to be most prominent in the 15-30 year age group, stimulant use in the 21-40 year old group, and prescription depressant use was more prevalent in the 45+ age group.

The National Transportation Safety Board and the National Institute on Drug Abuse investigated 168 fatal-to-the-driver trucking accidents in eight states over a one-year period in 1987-1988 (Crouch, Birky, Gust et al., 1993; National Trans-portation Safety Board, 1990a; National Transportation Safety Board, 1990b), and found a higher percentage positive for marijuana (13%) than did the above studies, and about the same percentage positive for cocaine (8%). They also found amphetamines in 7% of the drivers.

Several Canadian studies investigated drug use among fatally injured drivers. Cimbura, Lucas, Bennett, and Simpson (1982) presented the results of a compre-hensive drug study carried out on specimens from drivers and pedestrians fatally injured in Ontario. Toxicological analyses were regularly performed on blood and urine and occasionally on vitreous humor, stomach contents, and liver. The analytical procedures could detect and quantitate a wide variety of drugs including such illicit drugs as cannabis. With respect to drivers, alcohol was found in 57% of the study sample and drugs other than alcohol (including salicylates), in 26%. However, in only 9.5% of the drivers were psychoactive drugs (other than alco-hol) detected in the blood in concentrations that may adversely affect driving skills. Cannabinoids / THC and benzodiazepines accounted for a majority of the findings in this category, 15.7% for cannabinoids / THC and 5.7% for benzodiaze-pines. Narcotic analgesics were found in about 2% of the fatally injured drivers.

In a later study in Ontario, Cimbura, Lucas, Bennett, and Donelson (1990) examined the incidence and toxicological aspects of cannabis and ethanol in

1,394 fatally injured drivers and pedestrians in Ontario. The study subjects were 1,169 drivers and 225 pedestrians. THC was detected in the blood of 127 driver victims (10.9%) in concentrations ranging from 0.2 to 37 ng/ml, with a mean of 3.1 ± 5.0 ng/ml. For pedestrians, the incidence of THC in the blood was 7.6%. The incidence of THC in the driver victims in this study constituted an approximately threefold increase over the results of the earlier Ontario study. The authors attributed at least a part of the increase to inter-study differences in analytical methods for cannabinoids. In a more recent Canadian study, Mercer and Jeffery (1995) found that 13% of 227 tested fatally injured drivers in Vancouver, British Columbia were positive for marijuana and metabolites. Also, 4% were positive for cocaine, and 8% were positive for a CNS depressant (including 5% for diazepam). (These results were also reported in another paper noted on page 60.)

Drug presence in *non-fatally injured drivers* has been reported for patients admitted to trauma units in several locations. Dischinger and Birschbach (1990) examined the incidence of drugs (other than marijuana) seen in approximately 220 motor vehicle operators admitted to the Maryland Institute for Emergency Medical Services Systems over the period January-June 1988. They obtained positive test results for drugs other than alcohol as follows: amphetamines (0%); barbiturates (2.2%); cocaine (4.4%); methadone (0.4%); opiates (2.6%); and PCP (1.8%). Soderstrom, Triffilis, Shankar, et al. (1988) tested 393 car drivers only for alcohol and marijuana admitted to the same trauma unit in 1985-1986, finding 16% positive for marijuana alone, and 17% for marijuana plus alcohol.

Kirby, Maull, and Fain (1992) performed drug screens on 164 injured drivers admitted to a trauma center in Knoxville, Tennessee during early 1988. Drugs found were: marijuana (32%); benzodiazapine (12%); cocaine (5%); opiates (5%); amphetamines (2%); and barbiturates (1%). The King County, Washington study by Rivara and associates cited above also studied drug presence in 452 non-fatally injured motor vehicle occupants brought to an emergency room and then admitted to a hospital, finding that 25% of these subjects were positive for THC, and 8% were positive for cocaine. Again, there was no breakdown by type of occupant (driver or passenger).

Waller, Blow, Maio, et al. (1995) studied 717 drivers who came to two emergency rooms in southeastern Michigan for treatment following a motor vehicle crash. The study found that marijuana, cocaine, and/or opiates were present in 14% of the drivers. This study was unusual in that it is the only North American study of drugs in non-fatally injured drivers involving drivers who had presented at an emergency room but were *not necessarily admitted to a hospital* following initial examination and treatment.

In the most recent U.S. study of drugs among emergency room patients, Lillis, Good, Kwong, et al. (1999) found that 6.4% of 888 patients were positive for THC, 6.2% for cocaine or cocaine metabolite, and 4.1% for benzodiazepine. Few details about the study (including which emergency departments participated) are provided in the paper.

In a Canadian study, Stoduto, Vingilis, Kapur, et al. (1993) examined the incidence of alcohol and drugs in a sample of 339 drivers admitted to the Regional Trauma Unit at the Sunnybrook Health Science Center in Toronto, Ontario over a 37 month period. Drugs alone found were: marijuana (14%); benzodiazapines (12%); cocaine (5%); morphine (5%); codeine (4%); barbiturates (3%); pethidine (3%); diphenhydramine (2%); and pheniramine (2%). Drugs and alcohol combined were found in 17% of the drivers.

Foreign Studies

Pertinent more recent studies were conducted in Australia, Great Britain, Scandinavia, Belgium, France, The Netherlands, and Switzerland. (The reader is referred to a paper by Tornros (1990) for a review of earlier studies.) Three studies were concerned with *fatally injured drivers*. Two of these (Everest and Tunbridge, 1990; Everest, Tunbridge, and Widdop, 1988) were conducted in England and Wales. The studies found a wide variety of drugs, but only a small percentage of the drivers had used the drugs. In the first-cited study of 520 car drivers, such drugs were found in just 6.7% of the drivers: marijuana (2.3%); benzodiazepines (2.1%); anticonvulsants (0.4%); antihistamines (1.4%); and phenothiazines, antidepressants, and hypnotics (0.2% each). In the second-cited study, drugs of all types affecting the central nervous system were found in only 7.3% of the 330 drivers. Marijuana was present in approximately 1% of the drivers, and diazepam and/or its metabolite nordiazepam in less than 1% of the drivers. Other drugs were present in even smaller percentages of drivers.

A third study of fatally injured drivers (Gjerde, Beylich, and Morland, 1993) was conducted in Norway in 1989 and 1990 and examined the incidence of alcohol and other psychoactive drugs in 159 car drivers. The drugs found were: amphetamines (0.6%); antiepileptics (0.6%); barbiturates (0.0%); benzodiazepines (13.8%); marijuana (5.0%); cocaine (0.0%); muscle relaxants (1.3%); opiates (3.1%); and other drugs (0.6%). Of a total of 79 drivers fatally injured in single-vehicle accidents, 21.5% were positive for drugs other than alcohol.

In a study of the relative risk of driving while impaired by cannabis, Swann (2000) reported the results of tests of the presence of the active ingredient of marijuana, Delta-9-THC, in fatally injured drivers in New South Wales, Australia. He found that, in 4.3% of the 544 fatalities, cannabis was the only drug present, the driver was fully responsible for or contributed to his or her own death, and the levels of Delta-9-THC were sufficiently high to indicate that the driver was impaired.

Some other Australian studies have been concerned with drug presence in drivers in non-fatal crashes. A paper by Perl, Hodder, Havi, et al. (1990) reported drug test results of 612 drivers who had been hospitalized as a result of a traffic crash. They found that 37% of the drivers were positive for one or more of 56

different drugs found. Of interest here were: amphetamine / methamphetamine (1%); tranquilizers (2%); morphine (<1%); and marijuana (3%).

Two papers by Longo, Hunter, Lokan, et al. (2000a; 2000) documenting the results of a later Australian study used data on the tests of blood samples collected from 2,500 non-fatally injured drivers involved in road crashes. The blood samples were analyzed for the presence of alcohol, cannabinoids, benzodiazepines and stimulants. A total of 22.6% of drivers tested positive for at least one drug including alcohol. Either alone or in combination with other drugs, cannabinoids were found in 10.8% of the samples, benzodiazepines in 2.7% and stimulants in 1.3%. The authors reported that "a small number" of cannabinoid-positive drivers tested positive for tetrahydrocannabinol (THC, the main active ingredient in marijuana), but "most drivers" tested positive for the inactive metabolite.

Sjoegren, Bjoernstig, Eriksson, et al. (1997) reported the results of drug tests of 130 injured motor vehicle drivers who were hospitalized and 247 fatally injured drivers who were autopsied from May 1991 through December 1993. The tests were performed in Umea, Sweden and Gothenburg, Sweden. Benzodiazepines (3.5%), opiates (3.7%), and tetrahydrocannabinol (1.9%) were the most commonly drugs detected overall. Amphetamines, barbiturates, and other drugs were detected in smaller percentages of drivers.

A Belgian study (Schepens, Pauwels, Van Damme et al., 1998) sought to determine levels of alcohol and drugs of abuse in weekend drivers injured in car crashes. The study tested blood and urine samples of 211 drivers injured in weekend car crashes and involved five collaborating hospitals in Flanders. All injured weekend drivers admitted to the emergency units from July 1, 1994, to June 30, 1995, were included in the study sample. Twelve percent of the sampled drivers were positive for drugs, either in combination with alcohol or alone. Amphetamines were the most common drug (3.3%), followed by benzodiazepines (2.9%), cannabis (2.4%), and opiates (1.9%). Barbiturates and cocaine appeared less often, about 1% for each drug.

Also in Belgium, another paper documenting the BTTS study (Belgian Toxicology and Trauma Study) was performed between January 15th 1995 and June 15th 1996 (Charlier and Plomteux, 1998). The purpose was to investigate how frequently the drivers involved in road accidents were driving under the influence of psychotropic drugs. Two thousand fifty-three blood tests were performed of which 207 were in the Liege region. The national level data indicated presence of the following drugs: amphetamines (3.0%), barbiturates (1.3%), benzodiazepines (8.5%), cannabis (6.0%), cocaine (0.7%), opiates (1.1%), and propoxaphene (0.5%).

A French case-control study examined the prevalence of opiates, cocaine metabolites, cannabinoids and amphetamines in the urine of drivers injured in traffic crashes (Marquet, Delpla, Kerguelen et al., 1998). Subjects were from emergency departments of five hospitals and consisted of 296 "drivers" aged 18 to 35 and 278 non-crashed "patients" in the same age range. Screening for drugs in

urine was performed by fluorescence polarization immunoassays in each hospital. Each positive result was verified using gas chromatography-mass spectrometry (GC-MS), in a single laboratory. The tests showed cannabinoids (active ingredient) in 16% of the drivers, opiates in 10%, and cocaine and amphetamines in less than 1% each. By contrast, an earlier study of "road users" (car / truck drivers, motorcyclists, bicyclists, moped riders and pedestrians) in the Netherlands (Vis, 1988) found only 5% of the 282 subjects tested positive for "cannabinoids or opiates." (3.5% were positive for medicinal drugs taken from a list of the 50 most frequently prescribed drugs, mostly benzodiazepines or their metabolites.)

Ward and Dye (1999) summarized the results of 20 epidemiologic studies of cannabis involvement world-wide. Their results indicate that cannabis was detected in as few as 2.5% to as many as 38% of the crash-involved drivers. These wide differences are due to cultural differences in different countries (U.S., Jamaica, and Australia), time differences (from 1982 to 1998), the threshold criterion for drug presence (THC or metabolite and plasma concentration level used for indication of drug presence), and the definition of the subject sample (all fatalities vs. injured drivers only vs. fatal young males).

Finally, a study in New Zealand examined the long-term traffic-crash effects of cannabis use (Fergusson and Horwood, 2001). The study sought to determine the association between cannabis use and traffic accident risk among those who reported driving a motor vehicle between the ages of 18 and 21 years. The subjects were a birth cohort of 907 New Zealanders, and data were collected on annual frequency of cannabis use over the period from 18 to 21 years; annual rates of traffic crashes during the period 18-21 years; and measures of driver behaviors and characteristics. The researchers found statistically significant relationships between reported annual cannabis use and annual rates of crashes in which driver behaviors contributed to the crash, indicating that those using cannabis more than 50 times per year had estimated rates of crashes that were 1.6 times higher than the rate for non-users. However, when the crash rates were adjusted, driver behaviors and characteristics related to cannabis use (drink driving behavior, risky or illegal driving behaviors, driver attitudes, and driver sex) the association disappeared. The authors concluded that "although cannabis use was associated with increased risks of traffic accidents among members of this birth cohort, these increased risks appear to reflect the characteristics of the young people who used cannabis rather than the effects of cannabis use on driver performance."

The most striking feature of the foreign studies is the wide variance among the countries studied with respect to the percentages of drivers with given drugs. The two British studies and the Australian study found much smaller percentages of drivers positive for drugs of abuse than did the Norwegian study, which had percentages more in the range of those found in the North American studies.

DRUGS IN NON-CRASHED, ON-THE-ROAD DRIVERS

North American Studies

Studies of this type fell into two categories, (1) those that performed chemical tests of drivers stopped at some roadside location, and (2) those that surveyed drivers and asked them about their use of drugs prior to driving.

Only one U.S. study of the first category was found in our literature search, a study of 317 tractor-trailer truck drivers stopped at a truck weighing station in Brownsville, Tennessee during one week in December 1986 (Lund, Preusser, Blomberg et al., 1988). The presence of a wide variety of drugs was studied. Drugs and drug types found included: marijuana (15%); cocaine (2%); prescription stimulants (5%); and non-prescription stimulants (12%).

Several surveys have been conducted to obtain self-reports of driving after using drugs. In an earlier study, Hingson, Heeren, Mangione et al. (1982) performed anonymous random digit dialing telephone surveys of nearly 6,000 16-19 year old respondents in Massachusetts and upstate New York in 1979-1981. These surveys explored frequency of, among other things, driving after using marijuana. They found that 17% of the respondents reported driving at least once in the previous month after using marijuana, and 4% had done so after using "psychoactive drugs." In a 1982 survey of 623 seventh and tenth graders of age 16 or greater in the Boston, Massachusetts area, Wechsler, Rohman, Kotch, et al. (1984) found that 17% had driven after smoking marijuana during the school year just ending.

The National Household Survey on Drug Abuse (NHSDA) conducted by the Federal Government is another source of self-reported information on drinking, drug use, and driving in the United States. This survey has been conducted periodically since 1971, and the 1996 survey contained a special Driving Behaviors Module funded by NHTSA. A summary of the design and findings of the 1996 survey drawn from this module is contained in a government report (Townsend, Lane, Dewa et al., 1998).

The Driving Behaviors Module involved 11,847 personal interviews in a nationally representative sample of households. The respondents were individuals age 16 and older reporting that they had driven a motor vehicle in past 12 months, and whether they had driven within two hours after drug or alcohol use. The report by Townsend and associates indicated that 3.7% of the respondents had driven within the past 12 months after using marijuana, 1% had driven after using cocaine, and 1% had driven after using tranquilizers. Less than 1% was reported for stimulants and sedatives. Among those who had driven within two hours after using marijuana, about one in four had driven six or more times during the past month.

A more recent Canadian study reported the results of a roadside survey conducted from August 9 to August 29, 1999 in order to determine drug use among Quebec drivers (Dussault, Lemire, Bouchard et al., 2000). The survey

used a two-stage stratified sampling procedure, and included 147 sites representative of the Quebec driving population. During both daytime and nighttime, a total of 5,507 drivers participated in the survey, among which 95.9% provided a breath sample and 41.4% a urine sample. Among those who refused to provide a urine sample, 70.1% agreed to provide a saliva sample. Altogether, 82.5% of the drivers provided either a urine or a saliva sample. Regardless of time of day, a BAC above the illegal limit (.08) was found in 0.8% of the breath samples. During time period surveyed, drugs were found in the following proportions: cannabis (5.22%), benzodiazepines (3.66%), cocaine (1.09%), opiates (1.08%), barbiturates (0.35%), amphetamines (0.07%), PCP (0.03%).

Foreign Studies

Two studies were found, one in Germany and the other in Italy. The German study was documented in an article by Krueger, Schulz, and Magerl (1995), and the Italian study in an article by Zancaner and associates (1995). The data in the study by Krueger and associates were taken from a roadside survey in Germany in 1992. Chemical analyses were performed on 2,234 saliva samples, with the adjusted results indicating the following percentages of drivers nationwide testing positive for given drugs: benzodiazepines (2.7%); opiates (0.7%); marijuana (0.6%); barbiturates (0.6%); amphetamines (0.08%); and cocaine (0.01%).

The study by Zancaner and associates also involved a roadside survey. The survey was conducted in 1994-1995 to determine drug usage of drivers in the Veneto region of northeast Italy. According to the abstract in the paper, the study involved 1,237 drivers, including 265 who were suspected of driving under the influence of drugs. Both clinical and toxicological assessments were made, the latter involving chemical tests of both urine and blood. The study concluded that 10.6% of the subjects were "under the influence of drugs of abuse or psychoactive drugs," with the most frequently abused substances being (in order of frequency) cannabinoids, cocaine, amphetamines, opiates, benzodiazepines, and barbiturates. Unfortunately, the paper did not describe sample selection techniques, so we do not know what driver group is represented by the participating drivers.

The recent review by Ward and Dye (1999) of epidemiologic literature worldwide pertaining to cannabis and highway safety found that the few roadside surveys of THC in drivers have yielded fairly low rates: 4% in Canada in 1974, 1.2% in Italy in 1982, and only 0.6% (based on the less sensitive saliva test) in Germany in 1992–1994.

De Gier (2000) summarized the literature on the prevalence of illicit drugs in non-crashed drivers in different European countries. Although a total of 23 studies published in the time period 1990-1998 were collected, only four large-scale studies had large enough samples to be included in de Gier's summary. The results indicate that cannabis and opiates, the most frequently detected drugs, were detected in less than 1% in the general driver population. Benzodiazepines amounted to 3.6%.

Self-reported data are available from surveys in several countries. For example, Del Rio and Alvarez (1994) surveyed 1,500 Spanish drivers about their drug use and driving. Drugs for which responses were solicited were cannabis, amphetamines, tranquilizers, opiates, cocaine, psychedelic drugs, and inhalants. They found that, of these, cannabis was the drug used most frequently before driving in the past year (1.7% of the respondents), and that cocaine was next highest at 1%. Percentages for each of several other drugs were less than 0.5%. Lesch, Lentner, Mader, et al. (1989) surveyed 1,234 Austrian drivers about their use of several classes of drugs. Their data indicate that 2.6% were "possibly" using the following drugs while driving: CNS depressants, 2.4%; stimulants, 9.6%; analgesics or spasmolytics; and antidepressants or neuroleptics, less than 1%.

DRUG-CRASH RISK

North American Studies

Two U.S. studies were found that conducted a *formal* assessment of drug-crash risk. The first study (Terhune, Ippolito, Hendricks et al., 1992) used the responsibility-analysis approach[4] and found that no increased crash risk was associated with marijuana or cocaine alone, but that multiple drug use may be associated with increased responsibility.

In the second U.S. study, Leveille, Buchner, Koepsell, et al. (1994) used a matched case control study design to compare drug use habits of 234 crash-involved older drivers (65+ years old) in the Seattle, Washington area, relative to 447 control subjects matched on age, sex and county of residence who were not involved in a crash during that period. They failed to find an over-involvement in crashes for people taking benzodiazepines or sedating antihistamines, relative to people not taking this drug. Although they were aware that other studies found an association with crash rates, they were not able to provide a good explanation for their failure to find one, except to note that there is a large variance in the pro-longed effects of different benzodiazepines, and that their sample may have been too small to yield the expected effect. In this study there was an elevated crash risk for opioid users (RR=1.8). In both the crash-involved group and the control group, codeine was the most commonly used analgesic (61% and 51% of all analgesics, respectively). Note, however, that the time course and effects of orally ingested codeine may be very different from those of intravenously taken heroin.

Another U.S. study was performed by Ray et al. (1992) on a cohort of 16,262 drivers of age 65-84 registered in the Tennessee Medicaid program. They found that those taking benzodiazepines had a relative risk of an injury crash of 1.5, and

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[4] Responsibility analysis involves a clinical analysis of a crash to determine the odds that drug-positive drivers was responsible for a crash relative to the odds that drug-negative drivers were responsible for a crash.

those taking tricyclic antidepressants had a relative risk of 2.2. Persons taking high dosages of these drugs experienced higher relative risks, 2.4 for diazepam and 5.5 for amitriptyline. However, they did not find any increase in relative risk for people taking oral opioid analgesics.

Hemmelgarn, Suissa, Huang et al. (1997) conducted a cohort study of 224,734 Canadian drivers 67-84 years old. They obtained relative over-involvement rates of 1.45 (after initial use) and 1.26 (after continued use) in injury crashes for users of long-life benzodiazepines. However, they found no over-involvement for drivers using short-life benzodiazepines.

In another Canadian study, Neutel (1995) assessed the risk of hospitalization for injuries received in traffic accidents after a first prescription for benzodiazepines was filled. Saskatchewan Health supplied study populations of 78,000 adults who received benzodiazepine hypnotics, 148,000 who received benzodiazepine anxiolytics, and 98,000 control subjects. These populations were monitored for 2 months after the index prescription fill-date for hospitalizations due to traffic crashes. Analysis showed an odds ratio (OR) of 3.9 (1.9 to 8.3) for persons taking benzodiazepine hypnotics and an OR of 2.5 (1.2 to 5.2) for those taking Benzodiazepine anxiolytics, with regard to hospitalization due to traffic crashes within four weeks after the prescription was filled. Within two weeks after the prescription was filled, the OR had risen to 6.5 (1.9 to 22.4) for hypnotics and 5.6 (1.7 to 18.4) for anxiolytics. After 1 week, the ORs were even higher (9.1 and 13.5), but the confidence limits were wide. The highest risk groups were the youngest age group (20 to 39 years old) and males.

Foreign Studies

Drummer (1995) used data from some 1,000 fatal crashes Victoria, New South Wales, and Western Australia to develop fatal-crash risk factors for several drugs. Again, the responsibility analysis approach was used. Drummer computed odds ratios for drugs / no-drugs for each drug and found that only alcohol gave a statistically significant odds ratio greater than one (odds ratio=7.6, p <0.001). The odds ratio for cannabis approached significance (p=0.065) and was actually less than one (0.60), suggesting a beneficial effect of marijuana use. The odds ratios for drivers with stimulants, benzodiazepines, and opiates were 2.0 for each drug, but were not anywhere near statistical significance (p=0.217, 0.295, and 0.220, respectively).

The study by Longo, Hunter, Lokan et al. (2000) cited earlier in this report analyzed the causal role of alcohol, cannabinoids, benzodiazepines and stimulants in crashes involving 2,500 injured Australian drivers. The responsibility analysis approach also was used in the analysis. Benzodiazepine use was associated with higher culpability when those with very low concentrations were excluded (percentage ratio ≈ 3), but THC was not associated with increased culpability. Relatively few drivers tested positive for stimulants and there was no clear evidence of greater culpability.

However, Swann (2000) obtained quite different results with regard to THC in another Australian study of fatally injured drivers. In this study, the drivers were tested for the presence of Delta-9-THC, which only persists in the body for hours after use and allows the identification of drivers who were impaired by cannabis at the time of their death. By contrast, other Australian studies showing no culpability identified cannabis users by measuring Carboxy-THC, which can remain detectable in body fluids for weeks after cannabis use. Since impairment after cannabis use only persists for hours, the bulk of the cannabis users identified by Carboxy-THC would not be impaired, and responsibility studies did not show an increased risk of an accident for this group. These studies identified drivers who had consumed cannabis, not necessarily drivers who were impaired by cannabis.

Swann's study found that drivers who test positive to Delta-9-THC and have no other psychotropic drug or alcohol present have a relative risk (as shown by odds ratio) of 6. In 4.3% of the 544 fatalities, cannabis was the only drug present, the driver was fully responsible for or contributed to his or her own death, and the levels of Delta-9-THC were sufficiently high to indicate that the driver was impaired.

Barbone, McMahon, Davey, et al. (1998) analyzed the crash involvement of an extensive cohort of 40,400 UK residents who had benzodiazepine prescriptions during their three-year study period (1992-1995). In their sample, 19,386 were involved in a "first road accident" during that period, 1,731 were actual users of prescribed drugs, and 916 were users of benzodiazepines. Their principal findings and conclusions were that (1) users of anxiolytic benzodiazepines were at increased risk of experiencing crashes (average odds ratio = 1.62), and (2) crash risk was dose related. Also, the risk associated with benzodiazepine decreased with increasing driver's age (2.66 for people over 30) and increased when the driver also used alcohol (8.15 for those with positive BAC). Without alcohol, the odds ratio for a crash was 1.52 which was still significantly different from 1.0. On the other hand, no over-involvement was obtained for hypnotic benzodiazepines. This could be because (1) those are taken mostly at night before sleep; whereas anxiolytic benzodiazepines are taken during the day, often before driving, and (2) the case crossover method underestimates the effects the longer people have been taking the drug – and older people are often taking it chronically.

Marquet, Delpla, Kerguelen, Bremond, et al. (1998) performed a case-control study involving opiates, cocaine metabolites, cannabinoids, and amphetamines in France. Subjects were recruited from persons admitted for treatment in emergency departments of five hospitals nationwide and comprised 296 "cases" aged 18 to 35 and 278 non-traumatic "controls" in the same age range. Screening for drugs in urine was performed by fluorescence polarization immunoassays in each center, and each positive result was verified using gas chromatography-mass spectrometry (GC-MS), in a single laboratory. Statistical analysis comprised single-step logistic regression and simultaneously took account of confounding factors and the final differences in prevalence values between the two populations or different subgroups. The study's data indicate that only cannabinoids and

amphetamines had odds ratios differing significantly from 1, 1.94 for cannabin-oids and 0.57 for amphetamines (suggesting a beneficial effect).

Finally, the French Benzodiazepine/Driving Collaboration Group (1993) conducted a study that looked specifically at at-fault crash-involved drivers and pedestrians. Their results were consistent with those of the U.S. study by Leveille and associates summarized above, in the sense that they, too, failed to find an odds ratio significantly greater than 1.0 between injured drivers and pedestrians who were responsible for the crash vs. those who were not responsible for the crash, once the effects of BAC were held constant. One problem with their data is that most crashes were of young males drivers at night, while most of the benzo-diazepine users were adult females driving during the day – so the two groups had different risk levels and exposure to begin with.

DRUGS IN DRIVERS STOPPED OR ARRESTED FOR TRAFFIC VIOLA-TIONS

North American Studies

Several earlier studies dealt with drugs in drivers arrested in the United States for traffic violations. White, Clary, Graves, et al. (1981) reported the results of blood tests stemming from some 72,000 California drivers arrested for impaired driving in the 1970s. Percentages of tests indicating the presence of various classes of drugs in drivers with BACs < .10, were as follows: sedative/hypnotic, 30%-47%; phencyclidine (PCP), 79%; and morphine, 62%. Another study of drivers arrested in St. Louis, Missouri in the mid-1980s yielded the following percentages: phencyclidine, 47%; marijuana, 47%; benzodiazepines, 22%; barbiturates, 15%, opiates, 11%; and cocaine, 9% (Polkis, Maginn, and Barr, 1987). A third study in Washington, DC reported in 1992 found 39% of arrested drivers positive for cannabinoids, but only 9% positive for phencyclidine (Sutton and Paegle, 1992).

A fourth study of U.S. drivers arrested for traffic violations dealt with quite a different population (Brookoff, Cook, Williams et al., 1994). This population had the following characteristics:

- had been stopped by the police at night for exhibiting reckless driving;
- were suspected of impaired driving; and
- did not present any evidence of the presence of alcohol.

The study involved 175 consecutive cases of such drivers who were stopped on 46 consecutive summer nights in Memphis, Tennessee. Urine tests for cocaine or marijuana metabolites were performed for 150 of the drivers who agreed to provide a sample. These subjects also received a standard behavioral impairment evaluation which was later compared with the results of the drug screening test. The authors reported that 59% tested positive for either marijuana (33%), cocaine

(13%), or both (12%). The authors then state that those who tested positive were "intoxicated" by those drugs.

Taken at face value, these conclusions do not flow from the data presented and are misleading. First, although many of the subjects exhibited decrements on field sobriety tests, it is a leap of faith to say that they were "intoxicated" by those drugs. Second, in the text of the paper, it is reported that 30% of the marijuana positives were not confirmed by laboratory analysis, yet they appear as positives in the main table presented in the paper, the abstract, and in most of the discussion. Revising the conclusions to say that 59% (possibly adjusted down to 53% to reflect unconfirmed positives) of *drivers police suspected of drug-impaired driving* were positive for the marijuana or cocaine metabolites would make them more nearly in the same "ball park" as those flowing from the DEC evaluations of Preusser and associates and of Adler and Burns, summarized later below.

The most recent U.S. paper in our review (Walsh, Cangianelli, Buchan et al., 2000) reports the results of a study in which DUI Officers (Tampa Police Department, Tampa, Florida) were trained to use two rapid immunoassay devices to test driving-under-the-influence (DUI) suspects for recent drug use. In addition to routine determination of BAC, urine specimens were collected by police officers from persons placed under arrest for suspicion of DUI. Two hundred twenty-seven urine specimens were collected and analyzed by one of two "on-site" immunoassay kits being evaluated. The arresting officer conducted all analyses, but re-analyses were performed on all specimens testing positive on-site, and on 10% of on-site negatives. The results indicated that 30% also tested positive for one or more illegal drugs, and 55% of those who passed the Breathalyzer test with legal levels of alcohol (i.e., BAC<.08) were positive for one or more illegal drugs. Marijuana and cocaine were the primary drugs detected (19% and 16%, respectively). Narcotics and amphetamines were found in less than 1% of the specimens.

Another source of information about drugs in drivers arrested in the United States for traffic violations is NHTSA's Drug Evaluation and Classification (DEC) Program (See page 88). That program uses trained Drug Recognition Experts (DREs) to determine drug usage by looking for such signs and symptoms as dilated / constricted pupils, horizontal gaze nystagmus, and time estimates, among others. Four studies were found that documented evaluations of DEC programs. The most comprehensive of these was the study by Preusser, Ulmer, and Preusser, (1992) which evaluated DEC programs in selected sites in the states of Arizona, California, Colorado, New York, and Texas over various periods during 1986 to 1991. A total of 1,711 cases were evaluated, with laboratory tests available for 1,469 of these. The population dealt with was a subset of drivers already suspected of DWID. The data from this study suggest that such drivers who are classified as drug-impaired by DREs comprise some 1-3% of drivers arrested for DWI. Of the 1,469 drivers tested by a laboratory, the following drugs were found: marijuana (42%); CNS stimulants (36%); CNS depressants (16%); narcotic analgesics (13%); and PCP (5%).

Adler and Burns (1994) provided additional details on a subset of this population of drivers in their evaluation of the Arizona DEC program. In this study, 484 drivers examined by certified DREs from the Phoenix Police Department during January 1989 through May 1993 were laboratory-tested. Drugs found in the laboratory tests were: marijuana (34%); opiates (28%); cocaine (24%); benzodiazepines (22%); amphetamines (18%); barbiturates (7%); PCP (5%); and others drugs (30%).

The third DEC-documented program providing data on drug presence in drivers suspected of driving under the influence of drugs (DUID) was conducted in Virginia during the period 1988- 1990 (Jernigan, 1992). A total of 1,199 blood samples were submitted for analysis. The laboratory analysis found the following drugs: marijuana alone (17%); PCP alone (14%); other drugs alone (9%); and multiple drugs (18%). Finally, Tomaszewski, Kirk, Bingham, et al. (1996) evaluated the results of DRE assessments in Denver, Colorado, where urine screens found cannabis (67%), narcotics (5%), benzodiazepines / barbiturates (10%), stimulants (33%, including cocaine metabolites), and a few other drugs (<2%).

It should be kept in mind that the DEC subjects for whom the toxicological analyses were performed were drivers who (1) had been arrested for DUI, (2) were suspected of having been impaired by drugs other than alcohol, and (3) had been evaluated by the DREs. Thus, the above findings apply only to this restricted group of DUID suspects rather than to all drivers arrested for DUI.

Finally, we cite an interesting study by Marowitz (1994) which deals with a much different group of arrested drivers, but which, nevertheless, sheds some light on the overall drug-crash problem. This study compares the driving records of 106,214 persons arrested for drug offenses in California in 1989 with the records of 41,493 persons from the general driving population. Extensive statistical analyses were performed on the collected data, with careful attention to accounting for differences between the drug group and the non-drug group. No information was available on actual drug presence in the subjects.

The author concluded that drug arrestees committed significantly more (two to three times as many) *traffic violations* and significantly more (1.34 to 1.66 times as many) *traffic crashes* during the study period as did the general driving population. With respect to *traffic crashes*, the author concluded that drug arrestees had more traffic crashes for the year prior to the arrest and the year following the index arrest.

Other analyses were also conducted, including some aimed at estimating the effect of drugs on crash risk. Of these, the analysis of single-vehicle crashes (which are more likely to be caused by driver error) was especially interesting, indicating the drug-arrestees had a significantly higher percentage of such crashes than did the control group. The weighted mean number of single-vehicle crashes for all drug arrestees was 2.47 times that of the control group. The author also found that the drug arrestee group had significantly more injury/fatality crashes.

Nevertheless, the author was cautious about attributing increased traffic-crash risk to drug usage.

The extensive statistical analyses of the extremely large amount of data collected support the author's conclusions about increased traffic violations and crashes among drug arrestees. *However, there is insufficient evidence in this study to conclude that the higher number of traffic arrests and traffic crashes among drug arrestees is due to driving while impaired by drugs.* The author's findings on single-vehicle crashes and injury crashes not withstanding, support for the hypothesis that drugs used by drivers increases traffic-crash risk requires an unwarranted leap to the conclusion that the drug arrestees also drive more while impaired by drugs and that such drug-impaired driving is the cause of their increased number of traffic violations and crashes.

In sum, the studies discussed in this section do not provide much information about drug use among drivers in general who are stopped or arrested for traffic violations, although "ballpark" estimates for drivers arrested for DWI appear to be in the 1-10% range. However, these studies do indicate strongly that relatively high percentages of such drivers who are also suspected of "drugged" driving by the police and are evaluated by drug recognition experts are positive for a number of drugs that could impair driving performance. One small study in Tennessee also suggests that a large percentage of drivers interdicted by the police for other driving behaviors associated with drug impairment may also be positive for marijuana or cocaine. Finally, a very large study of driver records in California suggests that drivers arrested for a number of non-traffic drug-related offenses have increased numbers of traffic violations and traffic crashes.

Foreign Studies

The largest number of foreign studies in this category have been conducted in Norway. This review covers nine Norwegian studies based on data dating back to 1978.   Typically, these studies are based on analyses of blood samples from drivers suspected of driving while under the influence of alcohol or drugs. The samples were screened by the Norwegian National Institute of Forensic Toxicology. Unfortunately, the articles do not always describe the sampling protocols.

Bjorneboe, Bjorneboe, Bugge, et al. (1988) reported data from the years 1978, 1983 and 1986, indicating that there was a 19% increase in the number of samples submitted from 1983 to 1986. Of the 14,350 samples collected in 1986, 789 were tested for drugs. The authors state that 82% of these samples were found to be drug-positive compared to 54% and 88% of the 426 and 445 samples tested in 1978 and 1983, respectively. There was an increase in amphetamine use from 1978 to 1986. Benzodiazepines and marijuana levels were found in high levels during all the time periods. In 1987, the drugs found were: amphetamines (23%); diazepam (31%); flunitrazepam (25%); opiates (8%); marijuana (42%); and others (15%).

Christophersen, Bjorneboe, and Gjerde (1990) present data for the period November 1986 to February 1988. They indicate that the 270 samples analyzed for drugs were randomly selected from the drivers suspected of driving while under the influence of alcohol (DWI) or drugs (DWID). Drugs found were: amphetamines (4%); cocaine (0%); benzodiazepam (23%); and marijuana (47%). The percentages were about the same for drivers arrested for DWI and DWIDs.

Data from Gjerde, Christophersen, and Morland (1992) document some of the Norwegian findings for the 1989-1990 period which generated 380 blood analyses. Their report focuses on amphetamines which were found in 17% of the sample. The authors also examined impairment in 284 cases. Forty-nine of 81 amphetamine-positive drivers with no other drug were evaluated clinically for impairment, and 78% were found to be impaired. Data on the presence of other drugs are limited, with breakdowns being given only for 25 cases of arrests resulting from traffic crashes.

Later Norwegian data on drug presence among drivers suspected of drugged driving were collected in 1993 and are reported in two studies (Christophersen, Beylich, Bjorneboe et al., 1995; Morland, Beylich, Bjorneboe et al., 1995). In the first-cited study, the authors found drugs (primarily benzodiazepines, marijuana, amphetamines, and opiates) in 30% of the 1,197 suspected drivers tested. Of the 362 cases with drugs, 206 (57%) had benzodiazepines, 147 (41%) had THC, 81 (22%) had amphetamines, and 58 (16%) had opiates. As a percentage of total cases tested, these numbers are 17%, 12%, 7%, and 5%, respectively. The second-cited study was based on drug analyses of blood samples from 394 drivers suspected of drugged driving and involved in non-fatal crashes in Norway in 1993. The most prevalent drugs were benzodiazepines, cannabis, opiates, and amphetamine. Percentage of cases with positive results for such drugs were 13.7%, 7.6%, 4.1%, and 4.3%, respectively. The authors report evaluating all cases for possible impairment "based on drug concentrations," but do not describe their criteria for impairment. They state that more than 75% of the drug-positive drivers were "impaired" or "likely impaired."

The most recent Norwegian data indicate an increase in the number of drivers suspected by the police as being under the influence of drugs. A review by Christophersen and Morland (1997) found the most commonly detected drugs among 3,329 blood samples from drivers suspected by the police as driving under the influence of drugs were benzodiazepines (37%), THC (31%), amphetamine (30%), and narcotics (12%). Multi-drug use was frequently found (>60%). The occurrence of amphetamine also increased considerably from that found in prior studies. Christophersen and Morland (1997) concluded that the frequency of drugged drivers apprehended in roadside traffic was at least 10-fold higher in Norway than in most other countries, and that this over-representation was probably due "mainly to differences between national road traffic acts and the level of attention to the problem, and not to national differences in the prevalence of drugged driving."

Another study of the 1995 Norwegian data by Skurtveit, Christophersen, and Morland (1999) found that 71% of the drivers influenced by amphetamine in 1995 were drivers who had been arrested earlier because of impaired driving. More than 60% of the drivers apprehended in 1995 for driving under the influence of amphetamine had alcohol, THC or benzodiazepines in their initial sample. Christophersen, Abotnes, and Skurveit (2000) examined the 1995 data further for the prevalence of benzodiazepines in the 3,343 drivers who were apprehended by the police for suspicion of influence by drugs, finding that benzodiazepines (which represented some of the most frequently detected drugs) were detected in approximately 30% of the cases. In 8% of the cases, one benzodiazepine only was detected, and the blood drug concentrations in most of these cases were above therapeutic levels. In the remainder of the cases, one or more benzodiazepines were combined with illegal drug(s) (73%), other prescribed drugs (10%), or alcohol (15%).

Christophersen and associates also found the frequencies of benzodiazepines detected among drivers from different Norwegian counties correlated with benzodiazepine prescriptions from the same area. Further, 62% of the drivers had been arrested in the past 11 years for the same reason and there were 5.6 cases per rearrested driver. Alcohol was most frequently detected for those arrested for the first time before 1992, while benzodiazepines or illegal drugs were most frequently found for those with the first arrest during 1992 - 1995. They concluded that "our study shows that apprehended drivers using benzodiazepines are mainly represented by drug abusers, combining prescribed and illegal drugs and/or alcohol. A treatment program or other reactions, are thus necessary in addition to fines, prison penalty and suspension of driving license."

An earlier Norwegian study of rearrest recidivism (Gjerde, Bjorneboe, Bjorneboe et al., 1988; Gjerde, Bjorneboe, Christophersen et al., 1988) examined the driving records 100 drivers first arrested in 1983 and followed through 1988. Fifty of the 100 drivers were initially arrested for drunken driving and 50 for drugged driving. After three years, 34% of the drug group had recidivated compared to 20% of the drunk group. After five years, 50% of the drug group had recidivated compared to 32% of the drunk group.

Another Scandinavian study, this time in Denmark, (Christensen, Nielsen, and Nielsen, 1990) reviewed data on 461 cases that police had suspected of driving under the influence of drugs. Police provided the Medicolegal Council with the result of a clinical examination. Based on the results of the clinical examination, an estimation was made as to whether the driver would have been influenced by the drug. The samples were also screened for 100 different legal and illegal drugs. Apparently, the study was looking for a measure of the relative risk of various drug groups. This was done, we surmise, by comparing the percentage of crash-involved drug-driving suspects in a given drug group with the percentage of crash-involved drug-driving suspects in all drug groups.

Drugs found in drivers suspected of drugged driving were: benzodiazepines (65%); opiates (38%); and antidepressants and anticonvulsants (12.6% each).

From an analysis of their "relative-risk" data (relative risks not presented in the article) and a cursory review of the literature on drug effects on behavior, the authors concluded that there is ". . . a likely traffic danger by persons taking drugs, mainly barbiturates, benzodiazepines, and cyclic antidepressants," and that ". . . drivers under the influence of opiods do not contribute excessively to accidents." These conclusions should be regarded with some skepticism, not only because of a lack of information about specific drugs and chemical analysis methods, but also because of the highly selective nature of the samples. The results of the analyses of relative risk should definitely not be taken at face value, and the sweeping conclusions about "traffic danger" of various drug categories do not follow at all from the design and results of the study.

More recently, Steentoft and Worm (1996) investigated the frequency of benzodiazepines, morphine, amphetamine and cocaine in Danish traffic cases. The subjects were 294 drivers whose blood alcohol samples were negative. Drugs were detected in 27% of the cases, but analyses for drugs were only requested by the police in less than 10% of the cases. Twenty-three percent of the cases were positive for benzodiazepines with diazepam being by far the most frequently occurring drug followed by flunitrazepam. Morphine was detected in 7% of the cases, amphetamine in 5% and cocaine in only one case. Compared with a similar investigation in 1983, the frequency of benzodiazepines increased from 15% to 23%.

Holmgren, Loch, and Schubert (1985) analyzed the urine of Swedish drivers stopped by police for suspected DWI/DUID. Their analysis revealed that one third of the stopped drivers had some drugs-related substances in their urine – especially benzodiazepines and cannabis. None had any narcotics. Among those who were stopped but did not have detectable alcohol odor or detectable BAC levels, 91% had one or several "traffic hazardous drug substances in their body fluids." Of the legal drugs, the most common were benzodiazepines followed by analgesics. The most common illicit drugs were cannabis, followed by CNS stimulants and opiates. Of the drug-positive drivers, the police suspected 49% of DUID (rather than DWI), the medical doctors who interviewed them and took their urine suspected 78% of DUID, and a total of 99% of the drug-positive drivers were suspected of DUID by either or both the police and the doctors.

The prevalence of drugs in DWI/DUID suspects not only varies by country and culture, but also changes over time. Lillsunde, Korte, Michelson, et al. (1996) analyzed the blood of 298 Finnish drivers suspected of DWI/DUID in 1979 and 332 Finnish drivers suspected of DWI/DUID in 1993. They found drugs "hazardous to traffic safety" in 7.0% of the drivers in 1979 and in 26.8% of the drivers in 1993. Benzodiazepines were the most frequently detected drugs in both years: 6% of the cases in 1979, and 22.9% in 1993. Of the benzodiazepines, diazepam was the most common (75%), and oxazepam was the second (36%) (34% had multiple benzodiazepines). In half of the benzodiazepine cases, the concentration exceeded the limit that "can be evaluated as causing possible driving impairment". Interestingly, unlike other studies, they did not find an increase in benzodiazepine

frequency with age. In the 1993 sample, THC was detected in only 8 drivers, constituting 2.4% of the sample. Seven of these 8 drivers were under 35 years old. No narcotics were found in any drivers in either 1979 or 1993.

Perl, Hodder, Havi, et al. (1990) examined drug presence in 233 drivers arrested in 1987-1989 for drunk driving and suspected of drugged driving in New South Wales, Australia. The study found that 70% of the drivers were drug-positive with the following frequencies of occurrence for the various drugs: narcotics (43%); benzodiazepines (35%); marijuana (30%); and stimulants (10.5%). Additional data from 1989 through 1993 (Perl, Mascord, Moynham et al., 1995) on a wide variety of drugs found that about 80% of the drivers were drug-positive. A breakdown of 200 of the drug-positive cases by drug type indicated marijuana was the most common drug with 159 occurrences (79.5%). Opiates and other narcotic analgesics were found in 41% of the drivers, amphet-amines in 17%, and minor tranquilizers in 26%. Some of the characteristics of the study group are also presented.

In an interesting Swiss study, Augsberger and Rivier (1997) examined the epidemiologic and analytical laboratory records of 661 living drivers suspected of driving under the influence of a drug (DUID) during a 13-year period from 1982 to 1994. A traffic crash had occurred in 254 (40%) of the records, 273 (43%) drivers were suspected of DUID during police controls, and 95 (15%) drivers were suspected of DUID because of their erratic driving.   The authors found one or more psychoactive drugs (including alcohol) in 92.8% of the samples, includ-ing: cannabinoids (57%), opiates (36%), ethanol in (36%), benzodiazepines in (15%), cocaine (11%), methadone (10%), and amphetamines (4%). The majority (58%) of cases had two or more drugs in biological samples.

The last of the foreign studies in this category was conducted in Slovenia (Zorec-Karlovsek and Lokar, 1988). The authors report the use of alcohol, "trigonics" (not a term in use in this country), and benzodiazepines in Slovenian drivers arrested for suspected alcohol intoxication. Three hundred urine samples from the 36,613 arrestees were analyzed for the presence of psychotropic sub-stances by chromatographic methods, enzyme-immunological and color test methods. Benzodiazepine use was *confirmed* in 1%, opiates in 0.33%, and marijuana in 0.33% of the urine samples. Benzodiazepine use was *claimed* in 0.9% of the 3,105 individuals making statements about drug use but, interestingly, was *confirmed* in only about half of the lab-tested drivers *claiming* to have used benzodiazepines in their statements, with diazepam being the most frequently abused agent.

As with the U.S. studies, foreign studies of drugs in drivers stopped or arrested for traffic violations have been concerned primarily with such drivers who were already suspected of drug impairment prior to lab testing for drug presence. The lone exception seems to the Slovenian study which tested a sample of *all* drivers arrested for DWI and found that some 2% were positive for the psychotropic drugs screened for. The studies of drivers suspected of drugged driving are difficult to compare because of inconsistencies in defining drug classes but do

indicate high percentages of such drivers were positive for a number of drugs that could impair driving performance.

In all of the above studies, drug presence was measured given suspected impairment. However, none of these studies established a direct relationship between drug presence and specific impairment. To overcome this limitation, a study of the relationship between drug presence and specific behavioral impairments in drivers stopped for suspected traffic violations, is needed. Two studies that have done this are discussed below.

In the first study, Neuteboom and Zweipfenning (1984) tested the mental and physical performance of a sample of 906 Dutch drivers who were arrested for DWI/DUID and who admitted to medical officers that they took benzodiazepines. These drivers were most of the 3.2% of 38,203 drivers who were stopped for suspected impaired driving during 1981-1982. The authors compared these drivers' "performance" to that of drivers with identical BACs but without any drugs. The measures of performance were holistic measures of physical condition and mental condition as perceived by medical officers. Physical condition was noted in terms of gait ("steady" or "unsteady") and "mental condition" was noted in terms of behavior ("restrained" or "uncontrolled"). As expected, they found that the frequency of both physical and mental impairments increased with increasing BACs. More important for this report, however, they also found that among those drivers with BACs below .20, those who also took benzodiazepines were more likely to be impaired than those with alcohol only, but for drivers with BACs above .20, benzodiazepine did not seem to increase impairment beyond that already explained by alcohol alone. The authors also found that 9.7% of the 38,203 drivers had used drugs before driving.

Of these, 8.2% used "non-medical drugs," and of these, 40.2% used heroin (17.1%), methadone (20.1%), or both (3.0%); and 6.2% used cocaine (3.6%), and other stimulants (2.6%). Thus, of the total sample of suspected impaired drivers, only one-twentieth of one percent (0.005%) used a stimulant. This percent is probably an underestimate since all the drugs listed were based on admission or medical officers' opinions without the benefit of a chemical test. And, of the total sample of suspected impaired drivers, less than one-third of one percent (0.32%) used a narcotic.

In the second study, Kuitunen, Meririnne, and Seppala (1994) found that of 387,770 stopped for DWI/DUID in Finland over a period of 6 years (1987-1992), a total of 130 drivers tested positive for diazepam only (i.e., only one third of one percent of all stopped drivers!). These were further divided into two groups: chronic vs. acute drug users (based on the blood diazepam / nordiazepam ratio). All drivers were given the Finnish Clinical Test for Drunkenness (CTD), which is similar to the U.S. Standardized Field Sobriety Test (SFST). The CTD consists of a set of motor coordination tests (walking with open and closed eyes, observing the gait while turning, touching finger-to-finger, and collecting small objects), balance test (Romberg test with open and closed eyes) ocular saccadic movement (nystagmus), mental ability (backward counting by fixed subtraction, and time

orientation), and behavioral tests (speech, pulling oneself up, and overall behavior). Performance on each test was scored on a scale of 1-4, where 1 is normal performance and 4 is highly unstable or incorrect. The results showed that – except for slurred speech – chronic use of diazepam did not cause any significant impairments. On the other hand, acute use was significantly associated with impairment in most of the tests, including walking with open and with closed eyes, the pooled motor subtests, and the pooled behavioral subtests.

SUMMARY AND CONCLUSIONS

The epidemiologic literature on drugs and driving has continued to grow since the 1980 review of drugs and highway safety. However, most of the new studies are in two areas: drug presence in drivers involved in traffic crashes and drug presence in drivers suspected of drugged driving violations. Only one U.S. study was found that examined drug presence in on-the-road drivers not involved in crashes, and that study was concerned only with drivers of large trucks. No study assessed drug-crash risk by comparing the drug use of drivers who were just involved in crashes with that of a similar group of drivers who were not just involved in crashes. However, two U.S. studies and one Canadian study used data from driver records and surveys to determine risk factors associated with the use of selected drugs.

Figure 5-1: Percent of Fatally Injured Drivers Tested Positive for Various Drugs - Reviewed North American Studies
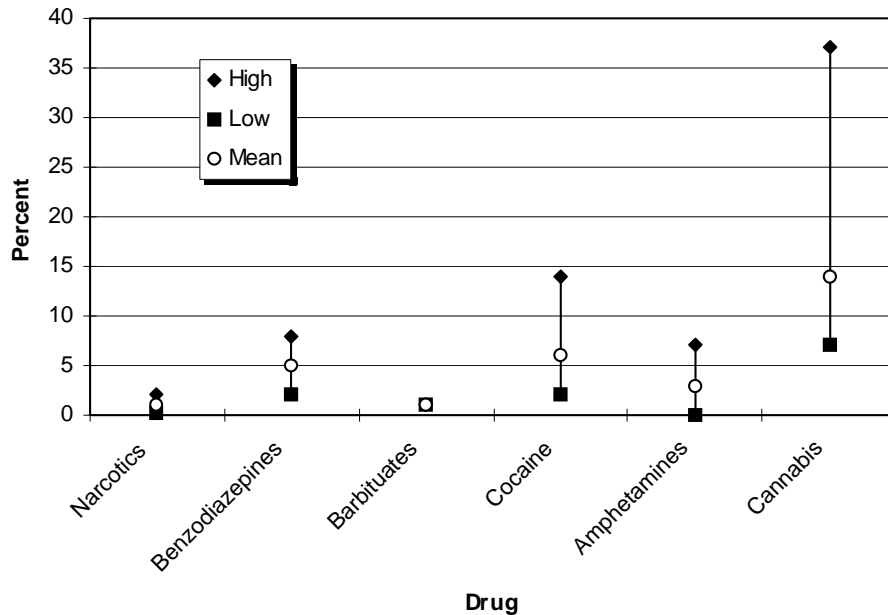
The literature indicates that chemical tests of *drivers in crashes* were performed most often for narcotics, benzodiazepines, barbiturates, cocaine, amphetamines, and cannabis. The range and means of the percentage of *fatally-injured drivers* who were positive for these drugs in the North American studies we reviewed are shown above in **Figure 5-1**. Cannabis had the highest percentages, ranging from 7% to 37% with a mean of 14%. The mean percentages of each of the other five drugs amounted to about 5% or less.

Figure 5-2 depicts how the mean percentages of drug-positive fatally injured drivers in North American studies compares with the mean percentages in foreign studies. Except for narcotics and barbiturates, the foreign studies show lower percentages than North American, considerably lower in the case of cannabis (14% for North America compared to only 2% for foreign). It should be kept in mind, however, that there were only four foreign studies in two countries (two in the United Kingdom, one in Australia, and one in Norway) in our review of drugs in fatally injured drivers, compared to 10 such studies in North America.

Figure 5-3 compares the mean percentages of drug-positive fatally injured drivers in North America with the mean percentages of drug-positive non-fatally injured drivers in North America. For most of the drugs, the percentages for non-fatally injured drivers are greater than the percentages for fatally injured drivers. This is opposite the case for alcohol for which the percentage of involvement of fatally-injured drivers is roughly twice that for non-fatally injured drivers.

We note that all but one of the seven reviewed North American studies of drugs in non-fatally injured drivers involved drivers who had presented at emergency rooms (usually at a trauma center) and had then been admitted to a hospital. The subjects in the other study (Waller, Blow, Maio et al., 1995) were *not necessarily admitted to a hospital* and were drug-positive only about half as often as those who had been admitted to a hospital. This admissions factor may be related to the very high percentage of drug involvement reported in trauma-center studies.

Few of the reviewed studies (one in Canada and four in other foreign countries) examined the percentages of various drug classes found in non-crash-involved drivers of vehicles of all types who were tested for drugs after being stopped by researchers. Only two drugs were found to be present in more than 1% of the drivers: benzodiazepines (4% in the Canadian study and a mean of 3% in the other foreign studies), and cannabis (5% in the Canadian study). Just one U.S. study dealt with drugs in drivers using the road but not involved in a crash, and its subjects were tractor-trailer truck drivers at one location in Tennessee. That study found that some 30% of the drivers were positive for either marijuana, cocaine, or stimulants.

Figure 5-2: Mean Percent of Fatally Injured Drivers Tested Positive for Various Drugs - Reviewed North American and Foreign Studies
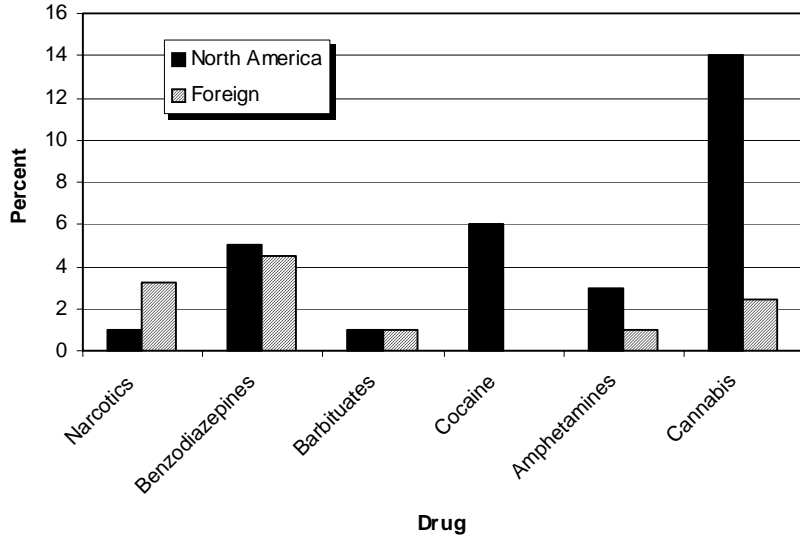
Figure 5-3: Mean Percent of Drivers Tested Positive for Various Drugs by Type of Injury - Reviewed North American Studies

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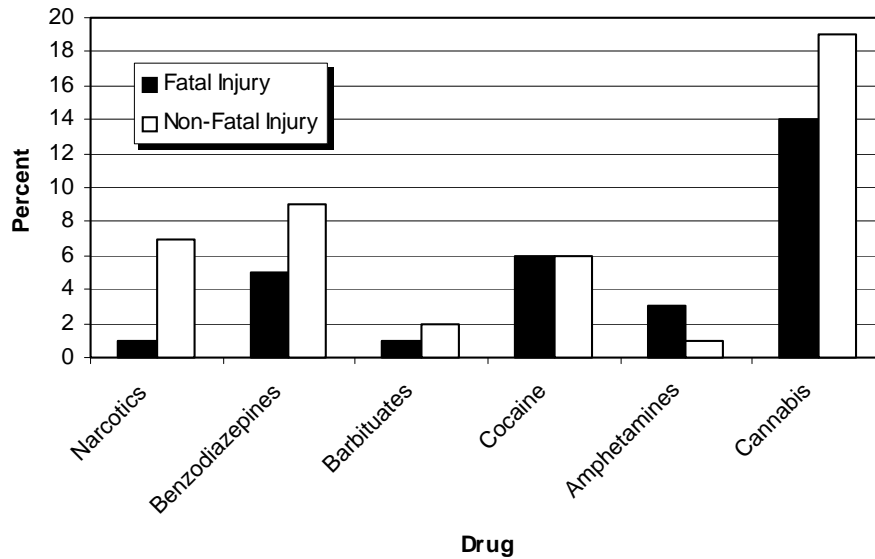
Drug-crash risk continues to be an unknown quantity. The single recent North American study addressing risk used the responsibility-analysis approach and found no increased fatal-crash risk associated with marijuana or cocaine alone, but a possible association of multiple drug use with increased crash responsibility. An Australian study also using the responsibility analysis approach found that only alcohol had a statistically significant increased risk of fatal-crash responsibility. The relative risk for cannabis (computed as an odds-ratio with p=0.065) was actually less than one, suggesting a beneficial effect of marijuana use. We note also in passing that the percentage of fatally-injured trailer-truck drivers in an eight-state sample who were drug-positive was roughly the same as that found in the Tennessee tractor-trailer truck drivers using the road but not involved in a crash.

In addition, a third, less formal, approach has been used wherein the percentage of a drug from a crash study (or studies) is compared with the percentage of a drug from a non-crash study. **Figure 5-4** is a synthesis of these approaches using data from the studies reviewed in this report. The bars labeled "single studies" are for studies using responsibility analysis (the first approach above) and information about drug use (the second approach) to calculate relative risk, and the bars labeled "separate studies" are for risk estimates based on data from separate studies for crash data and for non-crash data (approach three). The risk figures are for all the studies, North American and foreign, having the required data for vehicles and drivers in general, and are averages across studies for any given drug.

First, it is seen that data for the separate studies approach were available only for benzodiazepines and cannabis, and the risk figures for these two drugs were quite close to those obtained from single studies using one of the other two approaches. Second, none of the drugs was associated with very high relative risk, the maximum risk of about 2.0 occurring for benzodiazepines and cannabis, followed closely by narcotics at 1.5. CNS stimulants (including cocaine and amphetamines) were associated with either no increased relative risk (cocaine) or even decreased relative risk (other stimulants).

These figures provide only a rough idea of the magnitude of the drug-crash risk. Case-control studies of the type performed for alcohol-crash risk in the 1960s and 1970s (and one that is now being completed in a NHTSA-sponsored project) are needed for sharper estimates. Such a study for drugs would compare the percent of given drugs in crash-involved drivers with the percent in non-crash involved drivers at the times and places of the crashes. Because of difficulties in obtaining specimens for testing drug presence, such studies have not been conducted to-date, so only rough estimates of the type presented above are the best that can now be provided.

Figure 5-4: Relative Crash Risk of Various Drugs by Type of Study Averaged Across Reviewed Studies
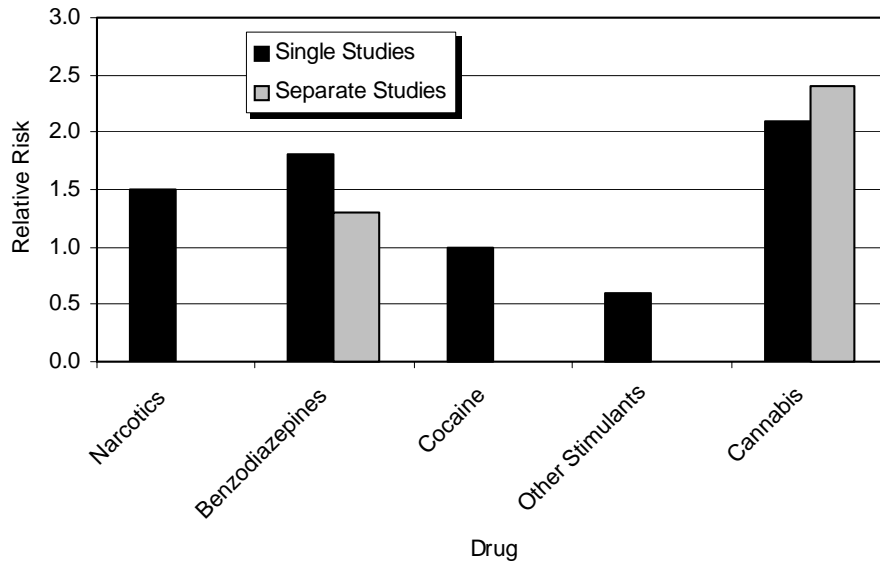
A number of studies have explored the question of drug presence in drivers stopped or arrested for traffic violations. These studies provide another perspective on the drug-crash problem, as such drivers have already been interdicted by police for suspected hazardous driving behavior, usually DWI. **Figure 5-5** is a compilation of the results of studies of this type that have been reviewed in this report. The percentages in the figure are averages across studies for the indicated drugs, presented separately for U.S. studies and foreign studies. Except for benzodiazepines, the percentages of drug-positive drivers were about the same in foreign studies as in U.S. studies, ranging from about 13% for barbiturates to 28% for cannabis. Benzodiazepines appeared in an average of 30% of drivers in foreign studies versus 14% in the U.S. studies. Some data were also available for PCP use in the U.S. (more in general use during the earlier studies), indicating an average of 16% for this drug. Only one foreign study (in Switzerland) had data for cocaine use (11%), and the U.S. studies indicated an average of about 16% of the drivers were positive for cocaine. These figures are notably higher than those for non-crashed drivers in general, for whom only cannabis and benzodiazepines were found in percentages exceeding 1%, and neither of those two drugs was found in more than 5% of the drivers.

Figure 5-5: Percentage of Drug-Positive Drivers Among Drivers Stopped or Arrested for DUID by Country
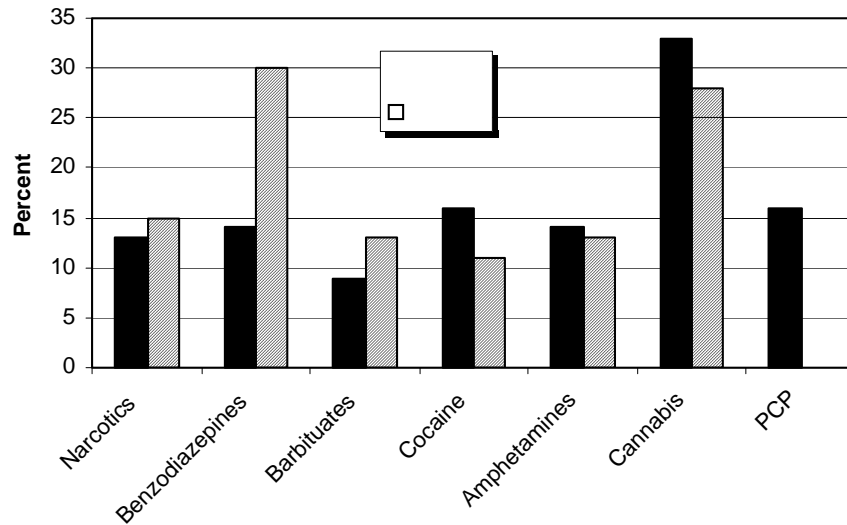
In sum, recent epidemiologic research indicates that:

- A significant amount of new information has been added to the pool of knowledge about the role of several classes of drugs in traffic crashes since the last state of knowledge update. However, gaps still exist on certain drug classes that are in widespread use, for example, antihistamines and antidepressants.
- Of the drugs appearing in epidemiologic studies of U.S. driver populations, marijuana has been found the most often by a wide margin. This should not be surprising, given the findings of the 2001 national household survey on drug abuse that 76% of current users of illicit drugs were users of marijuana (U.S. Department of Health and Human Services, 2002).
- For drugs that have been studied, the percentage of drug-positive drivers in crashes is much lower than the percentage of alcohol-positive drivers in crashes, but still not negligible.
- The role of drugs as a causal factor in traffic crashes involving drug-positive drivers is still not understood. Drug risk factors are still not known with acceptable precision, with some evidence suggesting little or no increase in crash risk at drug levels being detected by current chemical test procedures. Further, current research does not enable one to predict whether a driver testing positive for a drug, even at some measured level of concentration, was actually impaired by that drug at the time of crash.

This is in sharp contrast to alcohol where BAC measurements can provide a good estimate of impairment.

Another complicating factor is the role of drugs taken in combination with alcohol. For many drugs, a drug in combination with alcohol accounts for a significant percentage of the occurrences of that drug in crash victims. Waller et al. (1995) found that roughly one-half of the occurrences of drivers positive for marijuana, cocaine, and / or opiates had elevated BACs, and that the crashes of drivers testing positive for drugs alone were very similar to the crashes of drivers testing negative for both alcohol and drugs. This adds further doubts about the role of drugs in the impairment of crash-involved drivers, and suggests that it may be much smaller than had been suspected.

6 - COUNTERMEASURES FOR DRUG-IMPAIRED DRIVING

INTRODUCTION

Our review indicates that very little effort has been devoted to developing and operating countermeasures for drug-impaired driving. This is no doubt due, at least partially, to society's recognition that the magnitude of the drug-crash problem is much smaller (perhaps one to two orders of magnitude smaller) than that of the alcohol-crash problem. Consequently, society has responded rationally by putting forth less effort toward dealing with the drug-crash problem than it has toward dealing with the alcohol-crash problem.

Whereas there is now a large body of literature covering a range of counter-measure approaches for the alcohol-crash problem[5], nearly all of the very sparse literature on drug-crash countermeasures is concerned with a single approach. That approach involves the use of the Criminal Justice System to create, enforce, and adjudicate laws prohibiting drug-impaired driving, and to impose sanctions on persons convicted of violating such laws. Further, a single function of the Criminal Justice System, enforcement, has received virtually all of the attention in the literature. And, within the enforcement function, only activities involved in processing a motorist who has been stopped (for example, performing behavioral and chemical tests to determine impairment) are addressed in the literature.

This chapter discusses this literature as it pertains to countermeasures in the United States and in other countries as well.

DISCUSSION

Countermeasure Programs in the United States

For the most part, the enforcement of laws against drug-impaired driving has been performed in concert with the enforcement of laws against alcohol-impaired driving. In general, the laws are written in such a way as to proscribe driving while impaired by *any* substance, be it alcohol or some other drug. However, while in most states impairment is described rather precisely in terms of BAC for alcohol, it is described much more subjectively or not at all for other drugs. Some states limit the types of drugs covered in their law to controlled substances, that is, those substances that are controlled by the Federal government according to their potential for abuse and their accepted medical use in treatment. And in some

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[5] These approaches are discussed at length by Jones and Lacey (2001) in a recent update of the literature on the state of knowledge of the alcohol-crash problem.

states, the mere presence of illegal drugs constitutes a drug-driving violation. Also, some state laws explicitly prohibit driving while impaired by a combination of alcohol and other drugs.[6]

There are three main types of driving under the influence of drugs (DUID) statutes: (1) Statutes requiring that such a drug render a driver *incapable of driving safely*; (2) Statutes requiring that the drug *impair* the driver's ability to operate safely or require a driver to be *under the influence* or affected by an intoxicating drug; and (3) *zero tolerance per se laws* which make it a criminal offense to have an illicit drug or metabolite in the body (bodily fluids) while operating a motor vehicle.

All of the states save Texas and New York use the phrase "under the influence" in their DUID statutes. A total of fourteen states (Alabama, Arkansas, Illinois, Kansas, Nevada, Maryland, New Mexico, North Dakota, Oklahoma, Pennsylvania, South Dakota, Vermont, Wisconsin, and Wyoming) define the standard that constitutes "under the influence" within the body of the statute as "incapacity"; that is, the influence of the drug "renders the driver incapable of safely driving." Incapacity to drive safely is thus linked to the drug ingested, and the prosecutor must show a connection between drug ingestion and the incapacity of the driver.

Eight states (Arizona, Florida, Hawaii, Indiana, Kentucky, Montana, South Carolina, and Virginia) use the standard of impairment to define "under the influence" such that the influence impairs the person's driving abilities. This suggests a requirement of proof that is less stringent than one that renders the driver "incapable" of safely driving; nevertheless, the prosecutor must still prove that the impairment is directly related to the drug ingested.

As a result of the overall prevalence of drug abuse in the nation and the growing body of evidence of illegal drug use by drivers, eight states (Arizona, Georgia, Iowa, Illinois, Indiana, Minnesota, Rhode Island, and Utah) have enacted so-called "zero tolerance" laws which make it a criminal offense to operate a motor vehicle while having a drug or metabolite in one's body or bodily fluids. Under such statutes, individuals can be found guilty of violating the law if he/she were operating a motor vehicle while *any amount* of prohibited substances were present in his/her system.

The most extensive U.S. program dealing with the enforcement of drug-impaired driving laws is NHTSA's Drug Evaluation and Classification program (DEC). The DEC program was an outgrowth of a program developed by the Los Angeles, California Police Department (LAPD) in which officers were trained to become Drug Recognition Experts (DREs), and as such, to recognize behaviors and physiological states associated with seven categories of drugs, *viz.*, narcotic

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[6] A summary of state laws on driving while impaired *circa* January 2002 may be found in a NHTSA report (National Highway Traffic Safety Administration, 2002). A more recent comprehensive study of DUID laws in the United States may be found in a report by Walsh et al. (2002).

analgesics, CNS depressants, CNS stimulants, phencyclidine (PCP), cannabis, hallucinogens, and inhalants. A major objective of the program was to determine whether stopped drivers exhibiting the symptoms of alcohol impairment, but with low BACs, were impaired by some other drug. There are currently 36 states with DEC programs, and approximately 6,000 officers have received Drug Recognition Expert (DRE) training.

NHTSA sponsored two evaluations of the LAPD program, the first in collaboration with the National Institute on Drug Abuse (NIDA) and concerned with subject examination procedures (Bigelow, Bickel, Roache et al., 1985), and the second concerned with the program as a whole (Compton, 1986). The two evaluations found that LAPD's drug recognition procedure enabled police officers to recognize the symptoms of many types of drugs used by drivers suspected of drug use. Also, the DREs were able to correctly identify at least one drug in most of the suspects they judged to be impaired by drugs, and were able to correctly identify all of the drugs detected in about half of the suspects.

Evaluations of the DEC program in other jurisdictions were published in 1992, 1994, and 1996. A study by Preusser and associates (1992) evaluated DEC programs in selected sites in the states of Arizona, California, Colorado, New York, and Texas over various periods during 1986 to 1991, finding that most of the DRE opinions were confirmed by chemical tests and that most of the confirmed suspects were convicted. Jernigan (1992) performed a preliminary evaluation of Virginia's DEC program using data from the period 1988-1990. The program was a response to a 1988 Virginia law giving police officers the authority to require a driver to submit a blood sample to be tested for drugs. Jernigan concluded that the law helped increase arrests for DUI, but that DRE cases were no more likely to result in a conviction than non-DRE cases. Also, Jernigan found no evidence that the law reduced traffic crash injuries or fatalities.

Adler and Burns (1994) evaluated the Arizona DEC program using data from the January 1989 - May 1993 period. They found the DREs' decisions regarding the suspects, impairment and the drug categories creating the impairment to be highly accurate and concluded that the DEC program was a valid method for detecting and classifying drug-impaired drivers. Similar positive conclusions about DREs' ability to predict drugs in suspected impaired drivers were drawn in an evaluation of DRE performance in Denver, Colorado (Tomaszewski, Kirk, Bingham et al., 1996).

Recently, Shinar, Schechtman, and Compton (2000) evaluated DREs' actual performance in detecting drug impairment and in identifying the drug category causing the impairment. Four drug classes were tested in the study, cannabis, depressant, narcotic analgesic, and stimulant. Drug doses were administered by a nurse under the supervision of a physician, and the DREs were told that the subjects may be under the influence of none, one, or two or more drugs of any type except hallucinogens and inhalants. A total of 54 subjects participated in the experiment, and each subject was tested in six sessions over a period of six weeks spent as an in-patient. The tests were an abridged form of the standard DEC test

protocol, containing all of the elements of the standard test series except the interview with the arresting officer.

The study indicated that the DREs' ability to distinguish between subjects who were impaired and subjects who were not impaired was, in the words of the authors, "moderate at best." The DREs' ability to identify the drug class causing the impairment varied from "moderate" (for alprazolam) to "lower" (for cannabis and codeine) to "not better than chance" (for amphetamine). Further, the DREs relied on just one or two "pivotal" symptoms in making their diagnoses, rather than utilizing all of the information they had available as recommended by the DEC manual. The authors recommended that future training include formal models for synthesizing information and that the DEC protocol include the use of the interview and the arresting officer's report to check the results of the testing of physical signs and symptoms.

Countermeasure Programs in Other Countries

The literature we found deals almost entirely with European countries and indicates that, in most countries, a drugged driving violation requires proof of impairment due to the drug (ICADTS Working Group on Illegal drugs and Driving, 2000). However, Germany, Belgium, and Sweden have laws similar to the United States *per se* law for alcohol, prohibiting driving with the presence of any amount of illegal drug as determined by a chemical test of a body fluid.

The International Council on Alcohol, Drugs and Traffic Safety (ICADTS) has summarized the status of drugged driving countermeasure activity in Europe in its recent report referenced above. Information used in the report was obtained from a survey of ICADTS members and affiliates in 17 countries. Overall, as in the United States, countermeasures focus on enforcement of criminal statutes prohibiting drugged driving however defined. Clinical determination of impairment, roadside testing, laboratory testing, or all three may be required to establish impairment, depending on the country. A recent Belgian law explicitly allows the use of roadside urine tests as a component of its procedure to determine the presence of illicit drugs. Some countries (for example, Germany) have a procedure similar to the one used by DREs in the United States to determine impairment.

There is evidence that the drugged driving problem has begun to get more attention in Europe. Several initiatives involving multiple countries have been created and are examining the technological, legal, and operational aspects of drugged driving enforcement. Organizations include the Council of Europe (41 member states) and its Pompidou Group, founded to combat drug abuse and illicit trafficking in drugs; the European Monitoring Center for Drugs and Drug Addiction; and the European Transport Safety Council. Detailed recommendations for improving Criminal Justice System responses to the drugged driving problem in Europe are included in a recent report published by the Pompidou Group (Krueger, Perrine, Mettke et al., 1999).

SUMMARY AND CONCLUSIONS

The literature indicates that countermeasure approaches in the United States and Europe have involved the use of the Criminal Justice System to enforce drugged driving laws using methods similar to those used in enforcing DWI laws. The major emphasis appears to be the identification of impairment among stopped drivers using chemical tests and / or clinical assessments. In Europe, both approaches are used, the approach used depending on the country. In the United States, the emphasis is on the clinical approach as embodied in the Drug Evaluation and Classification program, (DEC).

Three evaluations of DEC found good agreement between assessments and chemical tests, but a more recent evaluation found problems in differentiating drivers who were impaired from drivers who were not impaired, and also found problems in identifying drug classes causing impairment.

Finally, we found no evaluations the impact of any drugged driving countermeasure on crashes, either in the United States or Europe. This might be expected, given the lack of any databases containing objective measures of the presence of drugs in crash-involved drivers.

7 - CONCLUSIONS AND RECOMMENDATIONS

Major conclusions and recommendations flowing from this review are presented in this chapter. The material is organized by subject-matter area as discussed in Chapters 3 through 6. Examples of documents supporting the specific conclusions are cited, and cross references to pages of this report discussing more general conclusions are provided.

DETECTION AND MEASUREMENT OF DRUGS IN DRIVERS

Conclusions

- A variety of specimens can be assayed for drugs, including urine, blood, sweat, saliva, and hair, among others. Each specimen is unique, and each offers different patterns of information about drug use over time (page 11).
- Most laboratories use immunoassay screening technology with gas chromatography-mass spectrometry (GC/MS) confirmation. Over the last 20 years the cost of using these technologies have become affordable, and most laboratories now have the equipment, the assays, and the expertise to identify the most commonly used drugs (page 14).
- While there have been significant improvements in laboratory assays for drugs of abuse, the value of such improvements to highway safety specifically is limited by an insufficient number of laboratories incorporating these improvements.
- The reliance solely on the forensic laboratory to assay all specimens in all cases limits the number drug-impaired driving cases that can be prosecuted, because there are simply not enough forensic resources currently available.
- Point-of-contact-testing (POCT) devices offer promise for alleviating this problem. For example, these POCT devices could be used by police officers to routinely screen DUI suspects for illegal drug use and obtain drug test results immediately, as they currently do with alcohol tests (page 15).
- Until there is adequate capability for rapid, cost-effective drug testing, many drugged drivers will not be identified or prosecuted.

Recommendations

- Federal and state agencies concerned with traffic safety should provide additional support to enhance forensic capabilities to detect and measure drugs in drivers.

- The forensic community should give more attention to the new POCT technology and work to integrate this technology with laboratory testing into a more efficient and cost-effective system for detecting and quantifying drugs other than alcohol in drivers.

EXPERIMENTAL RESEARCH

Selected literature on the effects of a wide range of drugs on performance of driving-related tasks and performance of actual driving tasks was reviewed. Classes of drugs considered were:

- narcotics,
- central nervous system (CNS) depressants,
- CNS stimulants,
- cannabis,
- antidepressants,
- antihistamines, and
- other drugs that have been investigated in a few individual studies.

Conclusions

- The amount of research in these classes varies widely, with the most attention given to CNS depressants and the least given to narcotics. We found essentially no experimental research on some other classes of drugs not listed above, for example, hallucinogens and inhalants.
- With respect to the acute effects of drugs, it appears that the following drug classes have a high potential for significant impairment of driving and driving-related performance:
  - ✓ narcotics (Stevenson, Pathria, Lamping, et al. (1986),
  - ✓ long-life benzodiazepines in therapeutic doses (Soames, 1982),
  - ✓ short-life benzodiazepines in high doses (Kunsman, Manno, Przekop et al., 1992),
  - ✓ barbiturates (Mintzer, Guarino, Kirk, et al. (1997)),
  - ✓ 1st generation H1 antihistamines (Moskowitz and Wilkinson, 2003; Starmer, 1985), and
  - ✓ certain anti-depressants, that is, amitriptyline, doxepin, and mianserin (see page 44).
- Drugs classes with a relatively low potential for significant impairment after acute usage are:
  - ✓ CNS stimulants (which actually may improve performance at low doses in some instances) (Ward, Kelly, Foltin, and Fischman, 1997),
  - ✓ 2nd generation H1 antihistamines (Starmer, 1985) , and most other anti-depressants (page 47).

- The literature suggests that acute use of cannabis has a moderate potential for impairment (Lamers and Ramaekers, 1999).
- Very few studies have examined the chronic and sub-chronic use of the above classes of drugs, and most of those that have suggest little effect on driving and driving-related performance.
- All-in-all, the literature supports the common-sense notion that drugs with a strong sedative action taken in the highest doses have the highest potential for significant impairment, while others have the lowest potential. Other meta-generalizations about which tasks and functions are impaired by which doses of which drugs cannot be made on the basis of the literature we examined.

Recommendations

- Current experimental research should be continued, with emphasis on newly emerging drugs with potential to impair driving performance.
- More research should be performed to determine the effect of chronic as well as acute use of drugs on the performance of realistic driving-related tasks. Such research should include both closed-course studies, and also simulator studies of the types possible in the National Advanced Driving Simulator at the University of Iowa.

EPIDEMIOLOGIC RESEARCH

Conclusions

- A significant amount of new information has been added to the pool of scientific knowledge about the role of several classes of drugs in traffic crashes since the last state of knowledge update. However, gaps still exist on certain drug classes that are in widespread use, for example, antihistamines and antidepressants.
- The literature suggests that the prevalence of the drugs that have been studied in driver populations, while not negligible, is much smaller than the prevalence of alcohol in such populations.
- The literature indicates that chemical tests of drivers in North American crashes were performed most often for narcotics, benzodiazepines, barbiturates, cocaine, amphetamines, and cannabis.
- Of these drugs, cannabis/marijuana has been found the most often by a wide margin. This should not be surprising, given the findings of the 2001 National Household Survey on Drug Abuse (U.S. Department of Health and Human Services, 2002) that 76% of current users of illicit drugs were users of this cannabis/marijuana.
- For fatally injured drivers, cannabis had the highest percentages testing positive, ranging from 7% to 37% with a mean of 14%. The mean per-

centages of each of the other five drugs amounted to about 5% or less (page 82).

■ Few of the reviewed studies examined the percentages of various drug classes found in non-crash-involved drivers (page 81). Only two drugs were found to be present in more than 1% of the drivers: benzodiazepines (4% in a Canadian study and a mean of 3% in other foreign studies), and cannabis (5% in the Canadian study).

■ Except for benzodiazepines, the percentages of drug-positive drivers suspected by the police of driving under the influence of drugs were about the same in foreign studies as in U.S. studies, ranging from an average of about 13% for barbiturates to 28% for cannabis (page 85). Benzodiazepines appeared in an average of 30% of suspected drivers tested in foreign studies versus 14% in the U.S. studies. Only one foreign study (in Switzerland) had data for cocaine use (11%), and the U.S. studies indicated an average of about 16% of the tested suspects were positive for cocaine.

■ The role of drugs as a causal factor in traffic crashes involving drug-positive drivers is still not understood. Drug risk factors are still not known with acceptable precision, with some evidence suggesting little or no increase in crash risk at drug levels being detected by current chemical test procedures. Available evidence (page 83) suggests a maximum risk factor of about 2.0 occurring for benzodiazepines and cannabis, followed closely by narcotics at 1.5. CNS stimulants (including cocaine and amphetamines) were associated with either no increased risk factor (cocaine) or even a decreased risk factor (other stimulants).

■ Current research does not enable one to predict with confidence whether a driver testing positive for a drug, even at some measured level of concentration, was actually impaired by that drug at the time of crash. This is in sharp contrast to alcohol where BAC measurements can provide a good estimate of impairment.

Recommendations

■ With respect to drug prevalence, the state of knowledge about the prevalence of drugs in traffic crashes in the U.S. should be updated periodically. Drugs of interest should include those currently in vogue among user populations.

■ With respect to drug-crash risk, a program of research should be undertaken to assess the traffic-crash risk associated with the potentially impairing drugs that current knowledge suggests are the most prevalent in serious traffic crashes in the United States. This research program should compare the drug use of drivers who were involved in crashes with that of a similar group of drivers who were not involved in crashes. The program should concentrate first on fatal crashes and should be of sufficient geographic scope to enable some reasonable assessment of the general magni-

tude of any drugged-driving problem nationwide. Clearly, such a research program poses some formidable difficulties, especially with respect to drugs in on-the-road, non-crash involved drivers. Nevertheless, work must begin if further progress is to be made in defining the drug-crash problem in this country.

COUNTERMEASURES FOR DRUG-IMPAIRED DRIVING

Conclusions

- Countermeasure approaches in the United States and Europe have involved the use of the Criminal Justice System to enforce drugged driving laws using methods similar to those used in enforcing alcohol-impaired driving laws.
- The major emphasis in these countermeasures is the identification of impairment among stopped drivers using chemical tests and / or clinical assessments.
- We found no evaluations of the impact of any drugged driving countermeasure on crashes, either in the United States or Europe. This might be expected, given the lack of any databases containing objective measures of the presence of drugs in crash-involved drivers.

Recommendations

- Determine the effect on traffic crashes of existing drug-impaired driving countermeasure programs in selected jurisdictions.
- Develop ways of improving the response of the Criminal Justice System to drug-impaired driving, including legislation, enforcement, adjudication, and sanctioning.
- Identify new, more innovative approaches to dealing with drug-impaired driving with initial emphasis on drug classes known to have higher potential for creating drug-crash risk.
- Increase the extent and intensity of research and development efforts to apply technology to drug-impaired driving.
- Provide more funding support to the efforts of operational agencies involved in current drug-impaired driving countermeasure efforts.
- Establish an integrated, long-term drug-impaired driving program at the federal level incorporating the above elements in a phased approach.

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