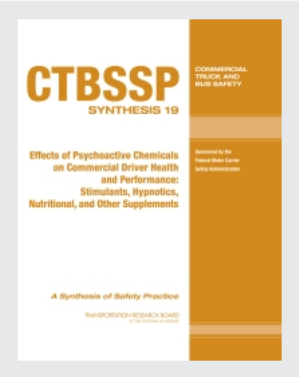

Effects of Psychoactive Chemicals on Commercial Driver Health and Performance: Stimulants, Hypnotics, Nutritional, and Other Supplements

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COMMERCIAL TRUCK AND BUS SAFETY SYNTHESIS PROGRAM

CTBSSP SYNTHESIS 19

Effects of Psychoactive Chemicals on Commercial Driver Health and Performance: Stimulants, Hypnotics, Nutritional, and Other Supplements

A Synthesis of Safety Practice

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TRANSPORTATION RESEARCH BOARD

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COMMERCIAL TRUCK AND BUS SAFETY SYNTHESIS PROGRAM

Safety is a principal focus of government agencies and private-sector organizations concerned with transportation. The Federal Motor Carrier Safety Administration (FMCSA) was established within the Department of Transportation on January 1, 2000, pursuant to the Motor Carrier Safety Improvement Act of 1999. Formerly a part of the Federal Highway Administration, the FMCSA's primary mission is to prevent commercial motor vehicle-related fatalities and injuries. Administration activities contribute to ensuring safety in motor carrier operations through strong enforcement of safety regulations, targeting high-risk carriers and commercial motor vehicle drivers; improving safety information systems and commercial motor vehicle technologies; strengthening commercial motor vehicle equipment and operating standards; and increasing safety awareness. To accomplish these activities, the Administration works with federal, state, and local enforcement agencies, the motor carrier industry, labor, safety interest groups, and others. In addition to safety, security-related issues are also receiving significant attention in light of the terrorist events of September 11, 2001.

Administrators, commercial truck and bus carriers, government regulators, and researchers often face problems for which information already exists, either in documented form or as undocumented experience and practice. This information may be fragmented, scattered, and underevaluated. As a consequence, full knowledge of what has been learned about a problem may not be brought to bear on its solution. Costly research findings may go unused, valuable experience may be overlooked, and due consideration may not be given to recommended practices for solving or alleviating the problem.

There is information available on nearly every subject of concern to commercial truck and bus safety. Much of it derives from research or from the work of practitioners faced with problems in their day-to-day work. To provide a systematic means for assembling and evaluating such useful information and to make it available to the commercial truck and bus industry, the Commercial Truck and Bus Safety Synthesis Program (CTBSSP) was established by the FMCSA to undertake a series of studies to search out and synthesize useful knowledge from all available sources and to prepare documented reports on current practices in the subject areas of concern. Reports from this endeavor constitute the CTBSSP Synthesis series, which collects and assembles the various forms of information into single concise documents pertaining to specific commercial truck and bus safety problems or sets of closely related problems

The CTBSSP, administered by the Transportation Research Board, began in early 2002 in support of the FMCSA's safety research programs. The program initiates two synthesis studies annually that address concerns in the area of commercial truck and bus safety. A synthesis report is a document that summarizes existing practice in a specific technical area based typically on a literature search and a survey of relevant organizations (e.g., state DOTs, enforcement agencies, commercial truck and bus companies, or other organizations appropriate for the specific topic). The primary users of the syntheses are practitioners who work on issues or problems using diverse approaches in their individual settings. The program is modeled after the successful synthesis programs currently operated as part of the National Cooperative Highway Research Program (NCHRP) and the Transit Cooperative Research Program (TCRP).

This synthesis series reports on various practices, making recommendations where appropriate. Each document is a compendium of the best knowledge available on measures found to be successful in resolving specific problems. To develop these syntheses in a comprehensive manner and to ensure inclusion of significant knowledge, available information assembled from numerous sources, including a large number of relevant organizations, is analyzed.

For each topic, the project objectives are (1) to locate and assemble documented information; (2) to learn what practice has been used for solving or alleviating problems; (3) to identify all ongoing research; (4) to learn what problems remain largely unsolved; and (5) to organize, evaluate, and document the useful information that is acquired. Each synthesis is an immediately useful document that records practices that were acceptable within the limitations of the knowledge available at the time of its preparation.

The CTBSSP is governed by a Program Oversight Panel consisting of individuals knowledgeable in the area of commercial truck and bus safety from a number of perspectives—commercial truck and bus carriers, key industry trade associations, state regulatory agencies, safety organizations, academia, and related federal agencies. Major responsibilities of the panel are to (1) provide general oversight of the CTBSSP and its procedures, (2) annually select synthesis topics, (3) refine synthesis scopes, (4) select researchers to prepare each synthesis, (5) review products, and (6) make publication recommendations.

Each year, potential synthesis topics are solicited through a broad industry-wide process. Based on the topics received, the Program Oversight Panel selects new synthesis topics based on the level of funding provided by the FMCSA. In late 2002, the Program Oversight Panel selected two task-order contractor teams through a competitive process to conduct syntheses for Fiscal Years 2003 through 2005.

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FOREWORD

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PREFACE

By Donna L. Vlasak
Senior Program Officer
Transportation
Research Board

This synthesis study identifies available information and research gaps relating to the use of chemical substances by commercial drivers and is intended to provide up-to-date information to inform decision makers about the near-, mid-, and long-range planning needs for research and educational outreach programs. Its aim is to assist the commercial transportation safety community and the Federal Motor Carrier Safety Administration (FMCSA) in addressing issues involving the proliferation and availability of psychoactive chemical substances.

Objectives included the provision of a narrative technical review of the scientific and analytical literature, summarizing what is documented about the effects of psychoactive chemicals on equipment operator performance; an extensive bibliographic reference listing of published literature on these topics; and two convenience surveys, offering information about gaps in knowledge and lessons learned. Appendixes present a description of the evidence available about the strength of a variety of chemical substances of which drivers appear to partake, as well as another supplemental bibliographic reading list of secondary source documents.

Results from the literature review and the two convenience surveys of small numbers of Commercial Driver Medical Examiners and of commercial vehicle stakeholders point to the need for development and provision of more detailed user-friendly information about the numerous chemicals, drugs, supplements, popular energy enhancement products, and other chemical substances that might impact commercial drivers' performance and health. Numerous areas where additional commercial motor vehicle safety issue studies may be called for are also identified in this report.

Dr. Gerald P. Krueger, Krueger Ergonomics Consultants, Alexandria, Virginia; Dr. Howard M. Leaman, Intermountain Sleep Disorders Center, Intermountain Health Care, Salt Lake City, Utah; and Gene Bergoffen of MaineWay Services, Fryeburg, Maine; with contributions from Daniel Murray and Racquel Pickett, American Transportation Research Institute, collected and synthesized the information and wrote the report. The Commercial Truck and Bus Safety Synthesis Program Oversight Committee members are acknowledged on the preceding page. This synthesis is an immediately useful document that records the practices that were acceptable within the limitations of the knowledge available at the time of its preparation. As progress in research and practice continues, new knowledge will be added to that now at hand.

CONTENTS

APPENDIXES D AND E OF THIS REPORT CAN BE FOUND AT: WWW.TRB.ORG, SEARCH ON “CTBSSP SYNTHESIS 19.”

EFFECTS OF PSYCHOACTIVE CHEMICALS ON COMMERCIAL DRIVER HEALTH AND PERFORMANCE: STIMULANTS, HYPNOTICS, NUTRITIONAL, AND OTHER SUPPLEMENTS

SUMMARY

This synthesis is the product of CTBSSP Project MC-19 and meets four principal objectives: (1) it provides a narrative technical review of the scientific and analytical literature, summarizing what is documented about the effects of psychoactive chemical substances on equipment operator performance, in particular insofar as the substances have application to commercial driver safety and health; (2) presents an extensive bibliographic listing of published literature on these topics; (3) suggests possible procedural discrepancies and information gaps in the examination process as it pertains to driver use of prescribed or self-administered medications by means of a convenience survey sampling of a small number of medical providers ($n = 23$) who conduct Commercial Driver Medical Examinations; and (4) by a convenience sample of more than 30 commercial carrier managers, reports views on access to user-friendly information and guidance regarding chemical substances that commercial drivers (employees) sometimes ingest.

Many medications produced by the pharmaceutical industry are prescription drugs and require licensed medical providers. Additionally, a modest number of over-the-counter medications to which drivers avail themselves can be used to self-medicate, whether drivers are diagnosed with an ailment or not. Third, an abundance of nutritional supplements and other readily available products (e.g., energy boost bars, drinks, and dietary measures) are being aggressively advertised to commercial drivers with representations that these products will help drivers maintain alertness on the job, sustain safe driving performance, and improve their health and well-being. Many substances in this latter category are prominently displayed for sale at convenience stores at highway rest and refueling stops, shopping centers, and elsewhere.

This synthesis provides information to assist the commercial transportation safety community and the FMCSA in addressing issues involving the proliferation and availability of numerous chemical substances available to and sometimes used by commercial drivers. The primary focus was to examine what is known about driver performance and/or driver health, as each may be positively or negatively affected by the proliferation of chemical substances (from whatever the source). Additional attention is given to what is known about the possible interaction effects resulting from taking two or more of these substances simultaneously, which drivers may occasionally do.

A voluminous amount of published scientific literature and hundreds of laboratory study reports pertinent to these topics were identified and reviewed during this synthesis project. The literature makes clear that numerous psychoactive medications (whether prescribed or available over the counter) and other readily available chemical substances have measurable effects on human operator performance of tasks akin to those of commercial drivers, and therefore may also impact job performance (both positively and negatively). Some hypnotics, stimulants, and nutritional supplements have been safely used in various sustained work settings. Successful applications of pharmaceutical intervention have primarily been witnessed in select military operations wherein limited use, acute administration of varying sleep aid and stimulant compounds is permitted with a goal to "get military operators through a particular

mission." Military policies require that such applications be in accordance with rigorous rules that include: (1) first establishing a person's exposure and experience with particular compounds, (2) obtaining voluntary consent to use the chemicals, and (3) the chemicals and medications be administered and used under close medical and safety supervision—conditions unlikely to be practical in commercial transportation work settings.

The synthesis literature review reaffirmed that there are only a few viable chemical substances that commercial drivers can legitimately and safely use as sleep aids (hypnotics) or as alertness enhancers (stimulants) during transportation operations and these are described in this report. The limited amount of research literature on many readily available nutritional supplements and other chemical substances likely to be ingested by commercial drivers makes more tenuous any assessments of their effects on worker performance and health. Because some of these supplements are widely sold in the United States, this synthesis concluded that more solid laboratory research work is needed on some, especially to delineate their possible effects on drivers' levels of alertness and safe driving performance.

Although companies employing commercial drivers may have policies regarding employee use of chemical substances, this synthesis report suggests there is a need for additional information to inform decision making by companies on chemical substances that might be used by commercial drivers, under various circumstances and operational use protocols.

The survey of a small number of Commercial Driver Medical Examiners suggests that further research could be helpful to inform development of an evidence-based list of approved medications and supplements to support more consistent practice among medical examiners with respect to drugs, medications, and issuing advice on driver fatigue countermeasures.

All three elements of this synthesis (literature review and two convenience surveys) point to the lack of detailed user-friendly information about the numerous chemicals, drugs, supplements, popular energy enhancement products, and other chemical substances that might have an impact on commercial drivers' performance and health. Many other areas where additional research may be called for also are identified in this report.

CHAPTER ONE

INTRODUCTION

BACKGROUND

Commercial truck, bus, and motorcoach drivers are expected to continually maintain full cognitive alertness while driving, and to sustain safe operating practices on our roadways, even during long highway trips. For decades there has been a common belief that many drivers in search of countermeasures to drowsy driving have taken to ingesting various chemical substances that might assist them in combating driver fatigue. Drivers occasionally may take a variety of psychoactive drugs, medications, sleep-inducing hypnotics, wakefulness-promoting stimulants, and a proliferation of other chemicals casually labeled as dietary and nutritional or health food supplements. Drivers do this to obtain adequate sleep during their off-duty hours or to boost their energy and prompt alertness while driving. The concern has been whether or not the individual or interactive and synergistic effects of such chemicals adversely affect their driving alertness, fatigue, performance, or health (Krueger CMV driver fatigue and wellness train-the-trainer experiences, 1996–2006; Krueger 2003, 2010).

Additionally, physicians and other health care providers legitimately prescribe various medications to drivers for treatment of diseases, illnesses, and a myriad of medical problems, including insomnia or sleep disorders. Commercial motor vehicle (CMV) drivers also may take a wide variety of over-the-counter (OTC) medications to self-treat their ailments, whether medically diagnosed or not. Drivers are known to consume medications to alleviate or ameliorate such physiological conditions as allergies, rhinitis, being overweight or obese, musculoskeletal discomfort, or for a variety of other medical conditions, including attempts at cessation of tobacco use and smoking. Of particular concern is the belief that even while taking medications to treat ailments some commercial drivers may also ingest various chemicals as contained in nutritional supplements (beverages, food bars, etc.) in an effort to boost energy levels, enhance alertness, or combat driver fatigue.

Two recent TRB publications identifying data gaps in truck and bus safety research determined that science-based information is needed to judge how drivers consuming such chemical substances affect their own driving alertness and performance, their sleep hygiene, fatigue management, and several basic health practices. A TRB Research Circular (Knipling 2007) presents a chapter on commercial driver health, wellness, and fitness (Krueger et al. 2007), and TRB *CTBSSP Synthesis 15: Health and Wellness Programs for Commercial Drivers* (Krueger et al. 2007b) identified the need for increased research on these topics. While developing the nation's second ten-year plan for a National Occupational Research Agenda, the National Institute for Occupational Safety and Health also identified the need for research to determine the relationship between the use of chemical substances by commercial drivers and any resultant short- and long-term health consequences or safety implications of such practices (National Institute for Occupational Safety and Health 2010).

As a result of this heightened attention to commercial drivers partaking of chemical substances, this synthesis project was initiated to provide information on the relationship between the use of psychoactive chemicals and driver performance, safety, and health.

OBJECTIVES AND SCOPE

There were four principal objectives for this synthesis:

1. To present a synopsis of a sizeable portion of the scientific literature on a wide variety of psychoactive chemical substances that sometimes are consumed by commercial drivers, particularly insofar as the substances may affect driver performance.
2. To provide an extensive bibliographic reference listing of published literature on these topics.
3. To administer a survey questionnaire to a small convenience sample of medical examiners inquiring about their anticipated actions with respect to their assessment of chemical substances pertinent to conduct Commercial Driver Medical Examinations (CDMEs).
4. To survey a sampling of motor carrier officials regarding their company policies about drivers using chemical substances.

This synthesis study identified available information and research needs relating to the use of chemical substances by commercial drivers and is intended to provide up-to-date information to inform decision making for near-, mid-, and long-range planning of research and educational outreach programs.

METHODOLOGY AND APPROACH

Literature Review

This synthesis provides a narrative review and description of much of what is known from the scientific literature about psychoactive chemicals that some commercial drivers at times ingest, and reports on the known and probable effects of such chemicals on operator performance, safety, and health. These substances include many prescription and self-administered medications, sleep-inducing hypnotics, wakefulness-promoting stimulants, and a large number of products best labeled as dietary and nutritional supplements, many of which contain psychoactive agents and are readily available over the counter in grocery and drug stores and at convenience stores located at fueling rest stops along the U.S. highways. Reports identified and reviewed included:

- Scientific journal articles presenting results of experiments involving psychoactive substances and equipment operator performance, as well as laboratory studies of generic performance and skill tests having a direct relationship to driving behavior (i.e., studies of drug effects on reaction time, psychomotor tracking, vigilance, judgment, decision making, and so on);
- Occupational health and safety reports pertaining directly to chemical substance use by transportation operators (commercial drivers, aviators, and others) and their performance;
- Rules and advisory guidelines from FMCSA published and available for use by the public and by CDMEs;
- Documents in the widely dispersed government-sponsored technical report literature, especially those of federal research organizations such as the U.S. military medical research and civil aeromedical research laboratories, the National Institutes of Health research institutes, and public health centers (e.g., National Institute of Drug Abuse); and
- A variety of professional scientific publications, textbook chapters, committee reports, symposia proceedings, position papers, and others that are largely produced outside the refereed journal literature.

Also provided as Appendix B is a brief analytical review of the medical and performance research that supports the current operational policy statements of the several U.S. military services, each of which permits selective, limited-time, operational use of psychoactive chemical substances to be taken by military personnel under highly controlled military circumstances. Such state-of-the-art/practice research portends the potential, but with significant accompanying cautions, for employing psychoactive chemicals for operational fatigue countermeasures in other work settings. It also anticipates discussion of whether such chemical substances would ever be usable in practice in select commercial transportation applications.

The literature review presented here is of the narrative type. It describes and appraises previous work, but does not specify methods by which any particular studies cited were identified, selected, and/or evaluated. Many of the citations are from scientific peer-reviewed journals. Many textbook chapters cited were written by leading scientists in their fields, whose knowledge of decades of their own and their peers' published works lends credibility to their synopsis on select topics. The choice of which articles to cite in this narrative review was largely determined by the synthesis team's judgment that a particular reference explicated the points being made or provided an alternative or clarifying viewpoint that the reader can seek out to suit his or her own interest in the topic. This review does not appraise all available research that may be relevant to a particular topic, but it does attempt to focus on key points and findings while citing numerous additional identified published studies in an extensive web-only Reference section (Appendix D), plus a web-only Bibliography (Appendix E) of citations that are useful, but not directly cited in the text.

This narrative presents an overview and some discussion of previous experimental and analytical works, selected because they explain effects of psychoactive chemicals (drugs, medications, supplements, and so on) on operator performance, particularly drug effects on psychomotor tracking, reaction time, judgment, and decision-making performance—all directly related to driving performance. The review suggests current gaps in knowledge on these topics. The information contained in the review can assist in developing a rationale for proposing new research that still remains to be accomplished. It also may be used to scope the types of interventions available to be included in more thorough analyses of the issues raised in the problem statements described earlier.

Bibliography of References Cited and Additional Literature

During the extensive search for, review, and critique of numerous scientific references for this synthesis, it became apparent that a great number of reports on psychoactive drugs and chemicals and performance are available (some previous review articles examined cite dozens, even hundreds of studies). Many of the reports identified here appear directly related to the task at hand, whereas many others only provide additional background or are only tangentially related. In both cases, the articles and reports are widely scattered. The references (web-only Appendix D) contain all of those citations actually cited in this report. It was deemed appropriate to provide at least a bibliographic listing of related citations in the belief that presenting them together in a single listing might save other researchers significant search time when

looking for additional publications pertinent to these topics. The Bibliography (web-only Appendix E) lists those citations determined to be sufficiently related to effects of psychoactive substances on performance and health to warrant including, that are not specifically mentioned in the text, but that could provide additional background.

Survey of Medical Examiners Performing Commercial Driver Medical Examinations

The synthesis team distributed a survey questionnaire about medications and drugs to a small convenience sample of 23 medical providers who administer CDMEs to commercial drivers seeking medical qualification and certification to drive commercial vehicles. The questionnaire was administered in two western geographical regions of the United States: 15 medical examiner responses were obtained in a Salt Lake City, Utah, survey; and 8 medical examiners were surveyed in Reno, Nevada.

The questionnaire asked these medical examiners about:

- Their anticipated certification decisions regarding chemical substances identified while performing medical qualification exams of CMV drivers,
- Their role in providing medical advice about driver alertness and combating fatigue,
- Their advice on the use of and identifiable hazards associated with ingesting chemical substances in the workplace, and
- Advice they might or might not give to CMV drivers and to their employers.

In particular, providers were asked about the certification actions and information resources relied on in making driver certification decisions. The survey questions asked of medical examiners also solicited suggestions for improvements in the administration and conduct of occupational medicine and CDME practices concerning use of chemical substances by drivers, and about the health and safety implications attached thereto. A summary of the questionnaire results is presented in chapter six of this synthesis report.

Survey of Commercial Carrier Policies on Driver Use of Chemical Substances

A structured interview questionnaire for use by CMV stakeholders (predominately truck carrier fleet managers, safety advocates, and other company officials) was administered to elicit key information about current policies, applications, and programs involving the use, or restriction of use, of psychoactive chemical substances by commercial drivers. The survey questionnaire asked specific questions about fleet managers' knowledge base, and about current company policies regarding driver use of stimulants, hypnotics, and nutritional supplements. The survey was sufficiently open-ended to gather information about experiences with current approaches, procedures, and safety policies in place, to identify problems, and to elicit proposed solutions regarding the use of chemical substances in the commercial transportation industries. Survey questions were specifically designed to cover the scope and objectives outlined previously. The survey questionnaire for motor carrier company officials was distributed by members of the American Transportation Research Institute (ATRI) to (1) the American Trucking Associations (ATA) Safety and Loss Prevention Management Council, (2) a Health and Wellness working group within that council, and (3) several wellness clinics located at travel centers that target over-the-road drivers. The participants consisted of safety and human resource personnel within the trucking industry, including motor carriers and allied professionals (e.g., motorcoach companies and health and wellness clinics). Motor carrier representatives were invited to participate by e-mail, which included an Internet link on ATRI's website where respondents could gain access to the online version of the Chemical Effects Survey.

There were 31 company responses. These companies employed a range of from 10 to a maximum of 6,200 drivers, with a company average of more than 800 drivers. Most respondents were truck carrier firms. The survey also netted responses from one commercial driver training company and one charter bus company. The specific questions posed in the survey are depicted in the context of the presentation of the results along with summary statistics for the surveys, and are described in chapter seven of this report.

CHAPTER TWO

RESEARCH ISSUES REGARDING PSYCHOACTIVE CHEMICALS

SYNTHESIS PROBLEM STATEMENT APPLIED TO THE LITERATURE REVIEW

This chapter outlines four issues that set the stage for literature review of chemical substances. This chapter also briefly describes the effects of alcohol (ethanol) on performance (about which much is known) to provide a *baseline* against which to judge research findings about effects of other chemicals and drugs. Subsequent chapters report on published findings describing the principal categories of psychoactive chemicals of direct pertinence to commercial driver performance and health. Chapter three reviews sleep-promoting substances, including hypnotics, and treatment medications prescribed for insomnia and other sleep disorders, as well as antihistamines often used to promote sleep. Chapter four covers stimulants and alertness compounds; those meant to keep one awake while working. Chapter five reviews dietary, nutritional, herbal, and energy boost compounds, or simply "supplements" that contain psychoactive components. Appendix A presents information on other psychoactive chemical substances within the U.S. National Institute of Drug Abuse's (NIDA's) list of addictive illicit drugs (drugs of abuse such as marijuana and cocaine), for which there is literature on performance effects, including research on the effects of such chemicals on driving performance. Although illicit drugs and other chemical substances do not warrant a viable role for operational use by commercial drivers, their occasional use by some commercial drivers is confirmed in employer random drug screening tests of drivers and by government-sponsored crash and accident investigation reports and statistics from numerous countries, including the United States.

DRUG DEFINITIONS AND CATEGORIZATION

The first issue is one of determining how to categorize or label the numerous classes of psychoactive chemical substances in this report. Chemicals, medications, or drugs could be identified in the way that medical practitioners consider them, as potential treatments for diseases, illnesses, and medical maladies or as prescription drugs or alternatively as non-prescription treatment drugs. Some drugs also could be classified as "controlled substances," which refers to their potential for abuse and physical as well as psychological dependence [see for example the extensive list of drugs, Schedules I through V, provided by the U.S. Drug Enforcement Administration (DEA) (CFR Title 21 Chapter II) and the lists of the Food and Drug Administration (FDA)]. Examples of Schedule II controlled substances include *opioids,* often prescribed to treat pain, and *stimulants,* sometimes prescribed for narcolepsy or Attention Deficit Hyperactivity Disorder (ADHD). *Depressants* may be prescribed to alleviate anxiety or for treatment of certain sleep disorders such as insomnia, and their controlled substance classification varies based on the factors identified earlier. Although there are concerns about how such drugs may affect driving performance, in some instances individuals afflicted by certain medical conditions may actually drive better when using the prescribed drugs, presumably because the drug treatment works to assist patients with their particular maladies (Barkley et al. 2005).

With some generalization, the effects of drugs can be discussed in terms of drug types or drug categories. For example, NIDA classifies *illicit drugs* into seven major drug categories on the basis of their psychoactive effects on the central nervous system (CNS). These classes and sample drugs within each class (derived from NIDA documents, 2006) are listed in Table 1. Narrative sections in this synthesis focus on several but not all of these drug categories.

The American Medical Association has published fairly extensive information on the driving-related effects of legally prescribed drugs (AMA 2003), as did the U.S. National Highway Traffic Safety Administration (NHTSA 2005) and the International Council on Alcohol, Drugs and Traffic Safety (ICADTS 2006). In reviewing such informative lists, NHTSA's David Shinar stated that "short of saying that all drugs are bad (and even that statement is not true) it is difficult to have a general discussion about drug effects on performance" (Shinar 2007b). This he says is because different drugs have different pharmacological properties that cause different physiological and physical signs and symptoms, and consequently have different effects on attitudes and behavior in general, and on driving-related attitudes and behaviors in particular. Shinar says it is nearly impossible and (fortunately) unnecessary to discuss separately each of the drugs in the categories identified in the governmental sanctioned lists mentioned above (Shinar 2005, 2007b).

The FMCSA has provided guidance for medical examiners of commercial drivers and rules governing the use of certain medications by commercial drivers. These are widely distributed and available on FMCSA websites, and will be discussed with each medication or substance; however, for most medications the FMCSA has given guidance based on the

TABLE 1
NIDA'S DRUG CLASSIFICATION

Drug Category	Examples of Drugs in Category
1. Cannabinoids	marijuana, hashish
2. CNS Depressants	barbiturates, benzodiazepines, flunitrazepam, GHB, methaqualone
3. Dissociative Anesthetics	ketamine, PCP, and analogs
4. Hallucinogens	LSD, mescaline, psilocybin
5. Opioids and Morphine Derivatives	codeine, fentanyl and analogs, heroin, morphine, opium, oxycodone HCL, hydrocodone bitartrate, acetaminophen
6. CNS Stimulants	amphetamines, methamphetamines, cocaine, MDMA, methylphenidate, nicotine (add in caffeine and ephedrine here even though they are not illegal)
7. Other Compounds	anabolic steroids, dextromethorphan, inhalants

Source: NIDA (2006).
PCP = Phencyclidine; HCL = hydrogen chloride; MDMA = 3,4-Methylenedioxymethamphetamine (ecstasy).

disease entity rather than on the medications themselves. The exceptions are insulin, 391.41(b)(3), which is forbidden for use by drivers of commercial vehicles (except by wavier under 49 CFR 391.64) and controlled substances, which are forbidden with the notable exception under 391.41(b)(12). Insulin will not be discussed in detail here.

Because this synthesis is primarily designed to serve the roadway safety community, the chemical substances described here could be categorized into clusters of the "most likely substances to be ingested by commercial drivers" and into additional categories that address "how these chemicals are likely to impact vehicle driver performance, safety, and health"; that is, as (1) hypnotics and sleep-promoting compounds; (2) stimulants and alertness-producing compounds; and (3) hormonal, herbal, dietary, and energy-boosting supplements. This latter scheme of chemical categorization is largely followed in this synthesis report. However, combinations of these categorizations are evident in the narrative descriptions presented, as some chemical substances belong to more than one of the several categories that fit their description.

CHEMICAL SUBSTANCE EFFECTS AND DRIVING PERFORMANCE

The second issue of importance for this synthesis is to present research findings about chemicals such that the results cited relate to commercial driver performance and health. Relating many of the published drug performance effects from laboratory studies to the performance of commercial drivers in on-the-road scenarios can be tenuous. Driving any ground vehicle involves many task elements, including physically handling the machinery (a car, bus, truck, or motorcycle) by steering, shifting gears, braking, staying within the lanes on the road (lane tracking), manipulating a vehicle through physical obstacles (e.g., highway, country, and city driving, in traffic, backing-up, and parking). The act of driving also involves many psychological and cognitive aspects of reasoning, judgment, decision making, reaction time, remaining continuously alert, paying attention to details, using keen visual perception during vigilance (visual, auditory, and kinesthetic vigilance), monitoring information, navigating between locations, responding to hazards on the road, and so on.

In the case of commercial drivers, other cognitive aspects of the job entail communication interactions with employers, dispatchers, shippers, and receivers. Bus and motorcoach drivers interact with passengers, charter and tour coordinators, tour-guide personnel, and others. In addition to the obvious physiological and cognitive tasks mentioned previously, many truck drivers carry out numerous physical activities and other ancillary duties involving pre-trip safety inspections, loading and unloading of cargo, securing loads (tarping, chaining, etc.), applying heavy chains to wheels, fueling, and other aspects of the job; whereas bus and motorcoach drivers, especially those involved in driving tour groups, often handle significant amounts of baggage (Krueger and Van Hemel 2001). Therefore, simply stating that a chemical substance or a drug affects performance readily invokes a question of what is implied by "performance" and how much of a drug effect is unacceptable for accomplishing individual tasks, completing a job, violating some safety principle, and risking adverse driving incidents.

In June 2005, TRB's Committee on Alcohol, Other Drugs and Transportation held a symposium to discuss the role of Drugs in Traffic. Many of the experts addressed involvement of drugs (licit and illicit) in traffic injuries and deaths. In his presentation on *Drug Effects and their Significance for Traffic Safety,* Shinar (2005) suggested that several implicit assumptions are usually made in the study of drugs and their effects on performance:

- Psychoactive drugs should have an effect not only on mood but also on cognitive and psychomotor functioning. Furthermore,

these effects should be reflected in performance on measures related to these functions (such as stability, reaction time, and speech) and should reflect some significant deviation from the norm.
- These cognitive changes are expected to be of such magnitude that they are both observable to a trained person and quantifiable with some standardized tests.
- Since driving is a fairly complex psychomotor and cognitive task, drug impairments should affect driving performance, usually in a negative manner.
- Individuals who take drugs often drive while under their influence, either because they do not appreciate their impairments or because their judgment is impaired.
- The resulting Driving Under the Influence of Drugs (DUI) problem can be dealt with in much the same way as DWI (Driving While Intoxicated—with ethanol) (Shinar 2005, p. 68).

The focus of this synthesis report is not on the role of drugs in crashes, but rather on what is known about the effects of chemicals on *driving performance* per se. This synthesis reviews, in brief, numerous scientific and research-oriented studies in the literature. For scientists and researchers defining theoretical and empirical questions to be answered through good basic laboratory and applied field experiments is key to determining the impact of chemical substances on sleep and alertness (loss or gain) and on work-related performance (enhancement or degradation). The most important factors are the "measures of performance" that provide the best understanding of the effects of various drugs or other chemical substances as they are related to driver performance on the roadway. It is not sufficient to report that an experimental study found that a single ingestion of a particular dose of a drug affects certain lab-based task performances that appear to be of little practical consequence, or in particular to report degradation in performance types that do not appear to have direct application to driving a truck or bus or motorcoach. For example, stating that a particular drug "alters a person's critical flicker fusion: CFF," or it "adversely affects psychomotor tracking, or reaction time, or judgment, or decision-making," without offering practical examples of how to apply the finding to vehicle driving circumstances necessitates a "stretch of inference" for understanding the implications regarding roadway safety.

One such set of scientific issues was delineated by Babkoff and Krueger (1992) who identified a set of at least eight plausible research protocol criteria (mostly based on measures of reaction time and measures of performance accuracy) that could be examined in laboratory experiments for deciding whether or not to use a stimulant to ameliorate performance degradation effects attributable to excessive sleep loss. This they identified in a paradigm with a particular aim of sustaining soldier performance during near continuous, around-the-clock military operations, where typically not much sleep is obtained by operational personnel. However, even reaction time measures are not always straightforward indications of equipment operator performance. Human factors research specialists involved in roadway crash investigations point to the many nuances and fine points of at least four identifiable stages associated with drivers' perception-response time immediately before becoming involved in a crash sequence, including detection, identification, decision, and response, demonstrating that in-depth assessments of driver reaction time (e.g., in accident reconstruction) are not a trivial matter (Olson 2007).

Not only is driving a fairly complex psychomotor and cognitive task, but it is a planned behavior. Different persons may drive from the same starting point to the same end point while employing different strategies; from the level of trip planning, to navigation, to reacting to specific situations. The additional involvement of chemical substances in driving scenarios make cause-and-effect analyses even more difficult, and can obfuscate even the simplest explanations of drug-induced response times reported in the experimental literature. For example, individuals under the effects of alcohol often experience overconfidence in their driving, and they speed. In contrast, individuals under the effects of marijuana often feel impaired and tend to drive slower. However, both drugs impair judgment and the ability to respond correctly to emergency situations (Shinar 2005, 2007b).

There is also the issue of individual differences in the variability of metabolism and behavioral responses or reaction effects to medications, drugs, and other chemicals. Metabolism and effects of drugs on individuals vary, in some cases quite significantly. That is, some people appear to manage satisfactorily with medications or chemical substances that in a similar situation would severely impair another person's behavioral responses (McBay 1997; Shinar 2007b).

These considerations raise important questions of how best to relate laboratory-based psychological and physiological performance measures to predicting driver behavior in "real world" situations on the highway. Obtaining and interpreting research quality measures of driving performance is not simple. From these descriptions it can be understood that determining that drugs in a laboratory experiment affect cognitive performance on generic psychological tasks is not always readily transferable to real-world roadway experiences. For example, some experiments have demonstrated that whereas low doses of a drug given to an experimental participant produce slight performance effects, these slight effects can actually become more pronounced when the nature of the task asked of research subjects is intensified, such as when the cognitive workload is increased or when subjects are asked to do multi-tasking (Pickworth et al. 1997; Shinar 2007). The "application leap" from lab-based findings to the "real world" is often not an easy one. Researchers usually agree however that if a drug adversely affects a fine-tuned measure of human performance (e.g., reaction time, signal detection, or precision tracking) in a controlled laboratory study it is reasonable to expect that such a drug-affected performance is not likely to improve while the individual is driving; performance on the road might even be worse.

DRUG AND ALCOHOL INFLUENCES IN CRASH STATISTICS

The third issue concerns assessing whether drug-involved automobile and truck and bus crash statistics can determine whether drugs or alcohol actually were factors in causing the crashes, or whether drugs merely were concomitantly *just present* at the time of the crashes. Numerous studies, reviews, and statistical treatises of highway accident reports document the large numbers of drivers, injured or dead in crashes, who had evidence of drugs or alcohol in their bodies. These determinations are often made through the analysis of blood or tissue samples taken soon after the crashes (e.g., NTSB 1990, 1995; DeGier 2005; TRB Committee on Alcohol and Other Drugs 2005). DeGier (2005), while focusing on medicinal drugs, cited numerous studies reporting traffic and drug statistics for 13 European countries, and indicated that the quest for knowledge on the prevalence of drugs other than alcohol in road traffic is hampered by methodological problems encountered with epidemiological studies of drugs and driving, including problems with sample collection and data collection procedures. DeGier estimated the presence of illicit drug use in the general driver population, at least in Europe, to be in the range of 1% to 5%, whereas the prevalence of medicinal drugs affecting driving performance is higher (5% to 10%). In an overview of studies on drug-impaired driving in the United States, Jones et al. (2003) reported that benzodiazepines were found to be present in 4% of noncrash-involved drivers. In a FMCSA research and analysis brief, Gruberg (2007) estimated that in 2005 1.7% of drivers with commercial driver's licenses (CDLs) used controlled substances, and 0.2% used alcohol [>0.04 BAC (breath alcohol concentrations)] while performing their duties.

In 1994, the U.S.DOT first issued regulations requiring testing of safety-sensitive employees in transportation industries "for use, in violation of law or Federal Regulation, of alcohol and drugs listed in the Controlled Substances Act" (*Federal Register* 1994). The DOT stated that drivers shall not use controlled substances, except when the use is pursuant to the instructions of a "physician who is familiar with the driver's medical history and assigned duties, and has advised the driver that the prescribed substance or drug will not adversely affect a driver's ability to safely operate a commercial motor vehicle" [391.41 (b)(12)]. The stated intent of the federal workplace drug testing program is/was to identify individuals who use "illegal substances" (*Federal Register* 1994; see also Section 503, Public Law 100-71). For safety-sensitive employees, including commercial drivers, random drug screening tests collect urine specimens that are tested for phencyclidine and cocaine (illegal drugs), and amphetamines, marijuana and opiates, which may be prescribed by a medical practitioner or taken without a prescription (Gruberg 2007). Regardless of jurisdiction, use of "medical marijuana" is prohibited by drivers of CMVs (FMCSA Frequently Asked Questions for Drug and Alcohol Compliance, FAQ: www.fmcsa.dot.gov/rules-regulations/topics/medical/faq.aspx.)

However, some other "legal drugs," which also are controlled substances and must be obtained by medical prescription, are known to have adverse effects on actual or simulated driving as well. Some of these include the hypnotics such as diazepam, flurazepam, and loprazolam, or various antidepressants and antihistamines. Many drugs, especially some prescribed medications, can influence vision, vigilance, and even impulsiveness. Problems such as driver fatigue, lack of attention, vigilance deficits, and suicidal and aggressive tendencies (singularly or in combination) can contribute to causing crashes. OTC medications available without prescriptions, but which are also known to be psychoactive, include drugs such as the antihistamines containing diphenhydramine (e.g., Benadryl®). Most likely because they are usually prescribed by a medical practitioner, not subject to high abuse potential, and not commonly used for "recreational purposes," tests for these drugs, and many others, are rarely performed on impaired ground vehicle drivers (whether commercial drivers or not). If two or more drugs are found in a vehicle driver, it is essential that the combined effect on performance be considered and evaluated (McBay 1997).

In civil and commercial aviation transportation, procedures have been put in place by the NTSB and the FAA's Civil Aeromedical Institute (CAMI) to do toxicological analyses of postmortem samples from pilot fatalities in aviation crashes to determine whether performance impairment from a medical condition(s) and/or drug and ethanol use was a contributing factor in a particular crash (Chaturvedi et al. 2005; Canfield et al. 2006; Botch and Johnson 2008). However, in both transportation communities (aviation and ground motor vehicle crash investigations) it is usually by inference that drug-crash causal conclusions are drawn and there is some uncertainty about the veracity of those conclusions.

The problem is exemplified by McBay (1997), who addressed issues of whether enough is known about the effects of drugs on driving performance to permit expert witnesses to testify in court cases about the likely impairment effects of drugs on a driver. Although McBay reported that adequate methods are available for the identification and determination of the *amount* of drugs through examination of blood, urine, hair, sweat, saliva, and other specimens taken from drivers shortly after crashes, the major problem is in relating the drug concentrations in the specimens to actual driving impairment. Specimens other than blood may be useful in determining drug use, but none is helpful in determining whether there was an active drug in the body that was *affecting driving performance at the time of a crash.* Interpretation of the effects produced at various concentrations of drugs in blood specimens depends on many factors not generally available to an expert witness for use as a basis for formulating acceptable scientific opinions. Some of the factors are: the impossibility of reliably back-calculating a concentration(s) to a prior time, individual differences in metabolism, single or chronic dosing, tolerance, withdrawal, inter- and intra-laboratory methods and variances, multiple drug use, method

of use, and the ranges of drug concentrations produced in different individuals ingesting the same size dose. Thus, although concentrations of drugs and metabolites in body fluids can be determined, unfortunately the concentrations of most drugs and their correlation with impairment or improvement of driving are not readily known (McBay 1997).

In 1983, a panel of medical experts reached a consensus concerning drug concentrations and driving impairment (which was reaffirmed in 1989). The panel reported that: "In order to establish that use of a drug results in impairment of driving skills and to justify a testing program to respond to this hazard, certain facts must be available:

1. The drug can be demonstrated in laboratory studies to produce a dose-related impairment of skills associated either with driving or with related psychomotor functions.
2. Concentrations of the drug and/or its metabolites in body fluids can be accurately and quantitatively measured and related to the degree of impairment produced.
3. Such impairment is confirmed by actual highway experience.
4. Simple behavioral tests such as can be done at the roadside by police officers with modest training can indicate the presence of such impairment to the satisfaction of the courts.
5. A range of concentrations of the drug can be incorporated in laws relating to impaired driving as ipso facto evidence" (Blanke et al. 1985; McBay 1989, 1997).

McBay, Shinar, and others appear to be in agreement that these criteria have been met for just one drug, ethanol (alcohol). The adverse effects of alcohol on driving performance have been well-established. Experts can testify to its effects based both on blood and BACs. However, most of what is known about alcohol and driving performance is not available for other drugs. It is not certain that these listed criteria can be met for most other drugs that now are of concern to highway safety (McBay 1997; Shinar 2007b).

DRUG INFLUENCES ON PERFORMANCE COMPARED WITH ALCOHOL EFFECTS

The three issues outlined previously serve as a segue to the fourth issue, which is that in the scientific literature, human performance researchers often report lab study drug effects by comparing them with the better-identified effects of ethanol (alcohol) on performance. Research on alcohol performance effects provides a "baseline" for relating and understanding how much impact other chemical substances have in affecting driver performance. This is so largely because:

- Predictable processing of alcohol (ethanol) in the body is well-understood;
- The effects of alcohol on so many forms of performance have been thoroughly studied and described; and
- Many individuals have experienced alcohol-impaired performance (even while driving), and thus they can more readily relate to comparisons employed to explain the effects of other chemical substances researched in experiments (Shinar 2007a).

Alcohol effects are so pervasive and consistent that the World Health Organization recommended that alcohol-related impairment serve as a benchmark for other impairments (Willette and Walsh 1983).

In his book, *Traffic Safety and Human Behavior*, Shinar wrote: "Despite the numerous studies on the effects of drugs on driving-related skills, on driving, and on crashes; and in contrast to the role of alcohol in driving and highway safety, we are amazingly ignorant of the role of drugs other than alcohol in driving and safety" (Shinar 2007a, p. 434). Shinar goes on to say there are two general reasons for this. Compared with other drugs, alcohol is a very simple drug. It spreads quickly and evenly throughout different body tissues so that blood alcohol levels correspond very well to concentrations of alcohol in the brain. There is a direct dose-response relationship so that the amount of impairment is directly related to the amount of alcohol that enters the blood and, consequently, the relationship between alcohol intake, blood concentration, and impairment is quite reliable and straightforward (Moskowitz 2002, 2007; Shinar 2007a). Alcohol affects just about every capacity we have including multiple perceptual, attentional, cognitive, decision, memory, and motor functions—all critical for safe driving (Ogden and Moskowitz 2004). The impairing effects can be demonstrated at very low alcohol levels and as the amount of alcohol in the blood rises, the number of functions that are impaired and degree of impairment increases (Moskowitz and Robinson 1988; Moskowitz and Fiorentino 2000; Ogden and Moskowitz 2004).

The psychomotor performance research literature reports a large number of alcohol and performance studies and a considerable number of those were done in driving simulators. Moskowitz and Robinson (1988) analyzed 177 studies that examined effects of low levels of alcohol (BAC levels of 0.10% or less) on driving-related functions and behaviors. They summarized their results in terms of the likelihood of impairment as a function of the BAC for nine different driving-related categories: reaction time, tracking, vigilance, divided attention, information processing, visual function, perception, psychomotor skills, and driving skill. Their significant findings were: (1) that alcohol in almost any amount impairs driving or driving-related skills, for all functions studied, and as the BAC level increases, impairment increases; (2) all aspects of driving behaviors studied are impaired as the BAC equals 0.10% or higher; and (3) there are differences among the cognitive functions in their sensitivity to alcohol. The most sensitive function—producing impairment at the lowest levels of BAC—was divided attention. Approximately 50% of the studies demonstrated impairment in divided attention at BAC less than 0.05%. The next most sensitive function

was tracking, with similar percentages showing impairment at BAC equal to 0.05%—significant because tracking and divided attention are inherent in almost all driving tasks. The least sensitive function was vigilance, with very few studies showing impairment below BAC equal to 0.08%. Moskowitz and Robinson concluded that although some individuals may be more affected by small concentrations than others, "there is no lower threshold level below which impairment does not exist for alcohol." A driving simulator study by Roehers et al. (1994) demonstrated that sleepiness and low-dose ethanol combine to impair simulated automobile driving, an impairment that extends beyond the point at which breath ethanol concentrations reach zero.

Similarly, Holloway (1994) examined 155 empirical studies (1985–1993) to reach three conclusions. First, sensitivity to the subjective intoxicating effects of alcohol was greater than that for all other performance classes and appeared to display a "threshold" with respect to BAC rather than the linear relation evident in performance data. Second, sensitivity to performance impairment in "controlled" performance and simulator tasks was greater than that for psychophysical functions of "automatic performance." Finally, a variety of task-, subject-, and environmental-characteristics or conditions were found to mediate the magnitude and sensitivity to alcohol effects, particularly at low doses. Holloway (1994) concluded that because alcohol sensitivity can vary from time to time, person to person, and situation to situation, the setting of a "safe" BAC will always be arbitrary, being based on low, but non-zero incidence of effects below that level.

Unlike establishing the relationship of alcohol to performance, the case for determining similar links of the presence of other drugs to that of cognitive performance (enhancements or decrements) is not so straightforward. Different sampling techniques and different residuals of the same drug have very different implications for the presence of drug impairment. For example, marijuana [with the active ingredient Tetrahydrocannabinol (THC)] is absorbed in fatty tissues and is then released back into the blood and urine as a metabolite that has no psychoactive effects (THC-COOH). Thus, detection of THC in the blood is indicative of recent ingestion; but detection of marijuana metabolites in the urine or the blood only indicates that marijuana has been used, and that the use could be as long as a few weeks ago. The second reason is that alcohol is a singular drug with specific repeatedly demonstrated effects, whereas other "drugs" as a generic category include different drugs that have different effects. These drugs are not evenly absorbed in all body tissues or even in the same brain centers; they do not necessarily have the same or similar physiological and behavioral effects and often do not exhibit a direct dose-response relationship.

Finally, drugs other than alcohol are often taken in combination (also in combination with alcohol) and depending on the specific drugs, the specific doses, and the user's past experience with drugs, they have joint effects that may be additive, synergistic, or antagonistic, and generally very difficult to predict (Shinar 2007a).

INFLUENCE OF CHEMICALS ON DRIVER PERFORMANCE

The three chapters that follow provide a brief capsule view of the voluminous material that could be cited to describe many psychoactive chemical substances that occasionally may be ingested by commercial drivers. More is known about the effects on performance of some of these chemicals than about others. In particular, less is known regarding newer drugs now available in the pharmaceutical marketplace, and this is especially true with regard to the nutritional supplements. From published research reports, short descriptions summarize a few pertinent points about each drug or medication and focus on aspects most pertinent to the occupation of commercial truck and bus and motorcoach drivers. Some augmented material for each chapter is relegated to supplemental coverage in the appendixes.

Selections of particular experimental studies and their results were made by the synthesis authors with the expectation that those cited provide reasonable explanations of what the general trends in the literature portend. In particular, the selections demonstrate the significance of several data gaps in our knowledge base about the effects of psychoactive substances on driving performance.

CHAPTER THREE

HYPNOTICS AND SLEEP-PROMOTING COMPOUNDS

INTRODUCTION TO SLEEP-PROMOTING CHEMICALS

The best approach to fostering driver alertness and managing driver fatigue on the roadway is to establish for oneself a suitable work–rest schedule, and especially to adhere to a *sleep management plan* during extended or sustained working hours, such as might be encountered during over-the-road operations (O'Neill et al. 1996; Orris et al. 2005). Obtaining adequate quantity and quality sleep is crucial for a commercial driver to maintain alertness on the job. Drivers preferably should obtain 7 to 8 h of sleep each 24-h day, which includes a contiguous stretch of at least 4 to 5 h of uninterrupted sleep (Krueger 1997, 2003; National Sleep Foundation 2010).

The FMCSA's current hours of service (HOS) rules for commercial drivers took effect in January 2004 (www.fmcsa.dot.gov). Specifically, the new HOS rules permit a 14-h work day (duty shift) of which 11 h can be driving, but require that on-duty periods be followed by 10 h off duty (the so-called 14–10 schedule). Under these HOS rules, drivers are expected to have more influence than they did previously for matching their working hours with known periodicities in circadian rhythm physiology, and thus make it more likely that drivers have the time during their weekly work schedules to obtain close to the desired 7 to 8 or more hours of restorative sleep per day.

If commercial drivers cannot obtain 7 to 8 h of continuous sleep, they then need to augment the sleep they obtain by taking supplemental naps each day (O'Neill et al. 1996; Krueger 1989, 1997, 2003). However, work schedules for many commercial drivers do not always permit enough time for them to take additional naps, nor are delivery schedules always conducive to drivers obtaining adequate sleep at the right physiological times on the 24-h clock (e.g., it is often difficult to sleep during daylight after driving through the dark hours of night). Applying what is known about sleep needs and circadian physiology is a key to maintaining driving alertness.

The topic also raises issues of whether as a part of their sleep management plan drivers might judiciously enact protocols employing hypnotic or sleep-promoting medications to induce and maintain sleep, and upon awakening to resume and maintain safe driving practices. This literature review covers performance effects regarding: (1) classes of depressant medications such as benzodiazepines and other closely allied prescription hypnotics, (2) prescription nonbenzodiazepine medications and others, (3) the synthetic sleep-inducing hormone melatonin, (4) first- and second-generation antihistamines, and (5) alcohol when used as a sleep-promoting chemical. After each separate compound is described, some literature reporting on performance effects is cited, and then a short assessment of its pertinence to the issues facing the commercial driving community is presented.

Performance after sleeping. The goal of many laboratory studies in the literature appeared to illustrate what performance detriments *hypnotics* produce when a person attempts to perform (e.g., to drive a vehicle) in the immediate period after taking a sleep-promoting drug, when sleep would be a naturally expected consequence. Such studies generally report decreased performance owing to effects of benzodiazepines, benzodiazepine-like drugs, first-generation antihistamines, tricyclic antidepressants, narcotic analgesics, and antipsychotics (O'Hanlon and DeGier 1986; Ramaekers 2003; Vermeeren 2004; DeGier 2005). Other studies addressed population-based driving risks following prescription use of both benzodiazepine and nonbenzodiazepine hypnotics. This synthesis literature review is less concerned with the "effects of hypnotics on driver performance soon after ingesting the medication" (under the influence), particularly if the driver's intention is to take a hypnotic to sleep. Rather, the goal here is to identify sleep-promoting compounds that can be used safely by commercial drivers to assist them to fall asleep; to help them obtain restful, restorative quantity and quality of sleep; and then to ensure that there are no important *sleep inertia aftereffects* soon after awakening and upon resuming driving (concern is for safe driving after awakening from drug-assisted sleep periods).

Sleep disorders. Some commercial drivers experience insomnia and other sleep maladies whether they have been medically diagnosed for them or not (e.g., Pack et al. 2002, 2006). Any sleep initiation or maintenance disorder that reduces sleep efficiency has the potential to affect transportation safety. Discussion of prescribing hypnotic medications for treatment of sleep disorders [e.g., insomnia, shiftwork sleep disorder (SWSD), sleep apnea, and restless legs syndrome] is beyond the scope of this report. For an outline of treatment protocols involving recommended drug doses for *sleep disturbed patients* who continue to drive, see DeGier (2005) and O'Hanlon and Volkerts (1986) whose work, done in conjunction with the activities of the ICADTS Working Group, was formulated as a guidance document, "Prescribing and Dispensing Guidelines for Medicinal Drugs affecting Driving Performance" (ICADTS 2001).

PRESCRIPTION BENZODIAZEPINES AS SLEEP-PROMOTING COMPOUNDS

Benzodiazepines are a family of depressant drugs in the class of anxiolytic agents. Because they produce CNS depression, benzodiazepines commonly have been prescribed for treating insomnia and anxiety. These hypnotics can be very effective in helping a person fall asleep more quickly, reduce the number of awakenings, and increase the total sleep time (Mendelson 2005). Benzodiazepines are classified as Schedule IV depressants under the Controlled Substances Act (U.S. DEA 2009). NIDA cites the five most frequently prescribed drugs in the benzodiazepine class as: lorazepam (Ativan), diazepam (Valium®), alprazolam (Xanax), temazepam (Restoril®), and clonazepam (Klonopin). Others include triazolam (Halcion®), chlordiazepoxide (Librium®), Dalmane, Doral, and ProSom. Flunitrazepam is unique among the benzodiazepines for being placed in Schedule IV, but having Schedule I penalties. The five most prescribed benzodiazepines are also some of the most frequently encountered drugs on the illicit drug market. NIDA lists the following as street names for benzodiazepines: candy, benzos, downers, nerve pills, sleeping pills, and tranks.

Benzodiazepines are marketed as mild or minor tranquilizers, sedatives, hypnotics, or anticonvulsants based to some extent on differences in their time-of-action, which ranges from less than 6 h to more than 24 h. Lorazepam (Ativan), alprazolam (Xanax), and oxazepam each have short half-lives. Some benzodiazepines have active metabolites that prolong their effects; therefore, for example, the half-life of diazepam is much longer, lasting up to 4 days. A drug's "half-life" refers to the period of time required for the concentration or amount of drug in the body to be reduced to exactly one-half. The elimination half-lives of benzodiazepines vary widely, from the relatively short-acting triazolam, to intermediate agents such as temazepam, to long-acting substances such as flurazepam, to clonazepam, the longest acting of the benzodiazepines (for details see Mendelson 2005). [See also the report of the FMCSA expert medical panel-psychiatric (Metzner et al. 2009), which presents a list of half-lives and a recommendation for blanket prohibition on commercial driving after use of benzodiazepines and nonbenzodiazepine hypnotics (within 7 half-lives)].

Application of low doses of the "shorter half-life" drugs may be useful as sleep aids for those doing shift work or for use in helping to induce sleep during long overseas flights, where the body has to adjust to a different time zone in a relatively short time (Reiter and Robinson 1995; Technical Cooperation Program 2001).

The literature on performance effects under the influence of benzodiazepines is covered later in this section following a description of a few of the newer sleep medications currently available.

NONBENZODIAZEPINE SLEEP-PROMOTING MEDICATIONS

Several other newer medications, essentially developed as alternatives to benzodiazepines, are currently being prescribed as sleep-promoting compounds. Some of the more common ones, often identified as nonbenzodiazepines, are described here: zolpidem, zaleplon, eszopiclone, ramelteon, and indiplon.

Zolpidem

Zolpidem produces sleep-inducing effects similar to those of benzodiazepines. In April 2007, the FDA approved 13 generic versions of zolpidem tartrate, a Schedule IV controlled substance. Zolpidem is available (as Ambien®, Stilnox®, Myslee®, and others) for oral administration in 5 mg and 10 mg tablets. Zolpidem has been prescribed for short-term treatment of sleep problems such as insomnia, because it acts on the brain to produce a calming effect (Scharf et al. 1994; Roth et al. 1995). Zolpidem may help a person fall asleep faster, stay asleep longer, and reduce the number of times that a person awakens during the night (Elie et al. 1999).

As a practical matter, with its relatively short half-life of 2.5 h, zolpidem is especially useful for promoting short- to moderate-length sleep durations (of 4 to 7 h) when shorter sleep opportunities occur at times that are not normally conducive to sleep, such as for taking daytime naps. Daytime naps are sometimes difficult to maintain, especially in individuals who are not sleep-deprived. The short half-life of zolpidem can provide short sleeps while minimizing the possibility of post-nap sleep inertia hangovers. Thus, zolpidem can make it feasible to take advantage of a nap without significantly lengthening the post-nap time needed to ensure that any drug effects have dissipated before being expected to resume performance of one's job. Some research results are a bit conflicting. Zolpidem of 10 mg at bedtime was reported to be free of cognitive performance impairment within 6.5 h (Nicholson and Pascoe 1988; Langtry and Benfield 1990; Balkin et al. 1992; Caldwell and Caldwell 1998). However, Vermeeren (2004) reported residual hangover effects such as sleepiness, and he reported that impaired psychomotor and cognitive performance after nighttime administration may persist into the next day, possibly impairing the ability of users to drive safely. Gustavsen et al. (2008) indicated that use of zolpidem may impair driving skills with a resultant risk of road traffic accidents, and called for cautious use by drivers.

In the military setting, Caldwell et al. (2009) suggested that zolpidem may be the optimal choice for sleep periods of less than 8 h and, if there were a possibility that the hypnotic-induced sleep period is likely to be unexpectedly shortened, zolpidem would be a better choice than temazepam. The U.S. Air Force has approved the use of zolpidem as one of the hypnotics referred to as "no-go pills"; however, prior

documented experience during ground testing with the drug is required before controlled administration. Even prior testing with such drugs however is no guarantee that they will work well in operations. Recently, when zolpidem successfully induced sleep in pilots before they controlled unmanned aerial vehicles in surge operations, side effects were reported in some crewmembers even though they had previously tested with the drug without side effects (Van Camp 2009). For results of military research employing zolpidem and other nonbenzodiazepines during lengthy operations and for use in transmeridian flight, see Caldwell et al. (2009).

Although zolpidem under the trade name Ambien® is one of the most widely prescribed sleeping pills in the United States, it is important to note that some users experience troublesome side effects. Ambien® users have reported instances of sleepwalking, as well as instances of eating or driving while not fully awake—with no memory of the events. Reports include Ambien® users "sleepwalking" into awkward circumstances and then not knowing how they got there. Ambien® use has shown up with some regularity as a factor in traffic arrests, and anecdotal stories relate how drivers later say they were *sleep-driving* and have no memory of taking the wheel after taking the drug. In 2007, the FDA cited reports of individuals getting out of bed after taking Ambien® and then driving their cars while not fully awake, often with no memory of the event—a phenomenon Shinar refers to as the "Ambien driver" (Shinar 2007b). The FDA stated that this behavior is more likely to occur when AmbienCR® (an extended release formulation) is taken with alcohol or other CNS depressants. The FDA warned that if a patient experiences such an episode, it should be reported to a physician immediately, because "sleep-driving" can be dangerous (www.fda.gov).

After similar reports of adverse events involving zolpidem marketed as Stilnox® occurred in Australia in 2007 and 2008, the Australian Therapeutic Goods Administration attached a Black Box warning to zolpidem, stating that "Zolpidem may be associated with potentially dangerous complex sleep-related behaviours which may include sleepwalking and other bizarre behaviours. Zolpidem is not to be taken with alcohol" (www.tga.gov.au). An additive effect of alcohol with zolpidem was demonstrated on memory and psychomotor performance (Isawa et al. 2000; Uchiumi et al. 2000). More recently, in April 2010, reports surfaced that some Royal Australian Air Force pilots were becoming addicted to Stilnox® because of repeated use of the drug over months-long deployments to Afghanistan (Parnel and Callinan 2010).

Assessment of zolpidem. The scientific literature does not currently provide sufficient explication of the potential of zolpidem-based products such as Ambien® and AmbienCR® for operational use with commercial driving. In particular there is a need to delineate any residual inertia hangover effects or effects on worker performance upon awakening from zolpidem-induced sleep periods, and to more fully explore the reported potential for adverse events such as sleepwalking, sleep-driving, and tendencies toward addiction following repeated use.

Zaleplon

Zaleplon, available as Sonata® or Starnoc®, is a sedative/hypnotic (pyrazolopyrimidine) that binds selectively to the benzodiazepine-l receptor. Zaleplon is rapidly absorbed after oral administration, with peak concentration being reached in about 1 h. The mean elimination half-life is around 1 h as well (Moore 2000). The claimed benefits are that zaleplon is effective in initiating sleep; it is mainly used to treat insomnia. Clinical trials of the hypnotic efficacy of zaleplon showed improvement in sleep initiation, particularly with a 20-mg dose (Elie et al. 1999; Fry et al. 2000), and it produced no hangover effects as early as 6 to 7 h later (Chagan and Cicero 1999). Zaleplon speeds sleep onset, reduces awakenings, and also is effective in sustaining sleep, thus increasing the total sleep time.

For times when one has difficulty falling asleep, it is recommended that zaleplon (usually 10 mg) be taken immediately before bedtime or even after a person has gone to bed. After zaleplon exerts its initial effects, the drug is subsequently and quickly eliminated in time for more natural physiological mechanisms to take over and maintain the remainder of the sleep period. Whitmore et al. (2004) found that when compared with a placebo, 10 mg of zaleplon effectively promoted sleep during the daytime even in well-rested individuals. Zaleplon allowed participants to obtain significantly more slow-wave sleep, as well as more sleep overall than under placebo. Performance was not adversely affected following a 3.5 h daytime sleep under zaleplon, nor were any undesirable symptoms determined (Whitmore et al. 2004). Although some studies (Paul et al. 2003) found that 10 mg of zaleplon impaired psychomotor performance for up to 2.25 h after ingestion, Hurst and Nobel (1999) reported 10 mg of zaleplon was without effect on cognitive performance measured 4 h after ingestion. To avoid any possible memory difficulties, zaleplon can be taken up to 4 h before planned time of arising and returning to work (Paul et al. 2004).

Caldwell et al. (2009) indicated that in the military setting, zaleplon (5–10 mg) may be the best choice for initiating very short naps (1 to 2 h) or for promoting slightly longer naps (2 to 4 h), which would otherwise be difficult to initiate and maintain during a period of sustained wakefulness. They also indicated that zaleplon (10 mg) may help hasten early-to-bed sleep onsets in personnel who are trying to ensure sufficient sleep before a very early start time the next morning (i.e., at 0400–0500 h). With regard to facilitating early report times, zaleplon is perhaps a preferred option to zolpidem; however, both compounds are important for the same reasons. With its ultra-short 1-h half-life, zaleplon is less likely to pose hazards in terms of residual drug effects that can exacerbate the drowsiness associated with the predawn awakening dictated by an early start time.

Assessment of zaleplon. Owing to its ultra-short 1-h half-life, zaleplon (e.g., Sonata®) offers potential in select commercial driving applications for initiating naps of from 1 to 4 h, especially at times when it is otherwise difficult to fall asleep. Research specific to the commercial driving needs must confirm that there are no residual inertia effects that could interfere with safe applications meeting the needs of the commercial driving sector.

Eszopiclone

Eszopiclone (Lunesta®) is an FDA-approved prescription drug used for treatment of insomnia. It is another new nonbenzodiazepine hypnotic agent, a derivative of the class of drugs known as cyclopyrrolones. Eszopiclone acts as an agonist on benzodiazepine receptors (Jufe 2007). It is rapidly absorbed after oral administration, with serum levels peaking between 1 and 1.3 h. The elimination half-life of eszopiclone is approximately 6 h, and it is extensively metabolized by oxidation and demethylation (Halas 2006). In terms of benzodiazepine receptor binding and relevant potency, 3 mg of eszopiclone is roughly equivalent to 10 mg of diazepam.

Lunesta® tablets contain 1 mg, 2 mg, or 3 mg of eszopiclone along with a variety of inactive ingredients. Lunesta® helps one to fall asleep quickly, so it is recommended that it be taken right before bedtime to be sure of having at least 8 h of sleep before becoming active. Lunesta® has a half-life of 5 to 6 h, making it a potential choice over temazepam, which has a longer half-life (Caldwell et al. 2009). Lunesta® demonstrated minimal residual drug effects after as little as 10 h post-dose (Leese et al. 2002). Lettieri et al. (2008) administered 3 mg of eszopiclone to 113 adults undergoing polysomnography for suspected sleep disorder breathing, and found that eszopiclone pre-medication significantly reduced sleep latency, improved sleep efficiency, reduced wake after sleep onset, and prolonged sleep time.

Eszopiclone (Lunesta®), along with zolpidem (Ambien®) and zaleplon (Sonata®), are the three most commonly prescribed sedative hypnotics in the United States. Pharmaceutical information includes advising users that until they know how they will react to Lunesta, Ambien, or Sonata, they should not drive or operate machinery. It is recommended that none of these three hypnotics be taken with alcohol, as it might increase the likelihood of adverse behavioral side effects such as sleep-driving.

Assessment of eszopiclone. For times when longer sleep opportunities are available; for example, during a driver's mandatory 34-h time off duty for a restart period, the new hypnotic compound eszopiclone (Lunesta®) might offer assistance in helping a driver to fall asleep. Even with its estimated half-life of from 5 to 6 h, some research findings identified minimal residual drug effects at 10 h post-dose. Subsequent additional research could confirm how long after drug dosing a commercial driver taking eszopiclone should refrain from driving. Remaining research issues include identifying any residual sleep inertia effects on performance from acute use and determining whether or not noteworthy effects occur with repeated use over a longer period of time (e.g., weeks or months).

Indiplon

Indiplon is a nonbenzodiazepine sedative/hypnotic that is relatively new to the marketplace. It is currently undergoing clinical trials and has been under consideration by the FDA. Caldwell et al. (2009) indicated that indiplon is chemically similar in structure to zaleplon and has a half-life of approximately 1.5 h. Indiplon, which is said to work by enhancing the action of the inhibitory neurotransmitter, γ-Aminobutyric acid (GABA), is like most other nonbenzodiazepine sedatives. It is being produced in a modified release formula that will extend its half-life to aid in sleep maintenance (Ebert et al. 2006). An indiplon immediate-release version targets sleep onset insomnia, whereas a modified-release form addresses sleep maintenance insomnia. Both forms of indiplon have shown improvement compared with a placebo in patients with primary insomnia in various areas of subjective and objective sleep measurements (Lankford and Ancoli-Israel 2007; Marrs 2008). Specifically, improvements in total sleep time, latency to persistent sleep, latency to sleep onset, wake after sleep onset, and sleep quality have been noted in clinical trials. So far, trials evaluating both indiplon immediate-release and modified-release have not identified any major serious adverse effects (Marrs 2008).

Assessment of indiplon. No research relating human operator performance and indiplon was located for this literature review. With its apparent ultra-short-half-life characteristics, indiplon may have potential for use in inducing sleep in some commercial driving scenarios. When the drug is available, conducting performance-oriented research on indiplon would be helpful to determine its effects.

Ramelteon

Ramelteon (Rozerem™), a novel oral hypnotic drug, is a nonscheduled prescription insomnia medication that can be prescribed for long-term use. Ramelteon promotes falling asleep and is used for treating insomnia. As opposed to targeting the GABA-A receptor, ramelteon acts by stimulating receptors for melatonin in the brain, by binding to the MT-1 and MT-2 receptors found in the suprachiasmatic nucleus (SCN), and thus helps to regulate the body's sleepwake cycle (Johnson et al. 2006; Owen 2006). Ramelteon therefore does not promote sleep by CNS depression. Research indicates that ramelteon is efficacious for sleep onset, but not for sleep maintenance (Lieberman 2007; Zammitt et al. 2007). Unlike many compounds used for treating insomnia, ramelteon is not addictive and is not a controlled substance. Ramelteon does not cause withdrawal symptoms or rebound insomnia when its use is stopped. Ramelteon was approved by the FDA in July 1995, and is available as Rozerem™ in 8 mg tablets.

With the exception of Rozerem™, all other prescription medications indicated for insomnia are classified as Schedule IV controlled substances by the DEA. It is recommended that ramelteon not be mixed with alcohol and that users avoid operating heavy machinery until they are sure how they react to the medication.

Johnson et al. (2006) did an experiment to compare ramelteon with triazolam and to placebo. Compared with placebo, ramelteon at 16, 80, and 160 mg (about 20 times the recommended dose) showed no significant effect on any of the subjective measures collected, including those related to potential for abuse. In the study, 79% of participants (11 of 14) identified the highest dose of ramelteon as placebo (meaning they could not differentiate). Similarly, compared with the placebo, ramelteon at any dose had no effect on any observer-rated or motor and cognitive performance measure. In contrast, triazolam showed dose-related effects on a wide range of subject-rated, observer-rated, and motor and cognitive performance measures, consistent with its profile as a sedative drug with abuse liability. Johnson et al. (2006) concluded that ramelteon may represent a useful alternative to existing insomnia medications.

Because of its action on melatonin receptors, which help control the body's circadian phase, ramelteon has been used to facilitate phase advance in circadian rhythm disorders such as jet lag and shift work (see section on melatonin). Circadian factors are recognized as an important factor in road accidents (Gertler et al. 2002; Richardson et al. 2008).

Assessment of ramelteon. No studies of human performance as affected by ramelteon were located for this literature review. More research is needed with this new, potentially promising hypnotic compound.

SLEEP-PROMOTING COMPOUNDS AND DRIVING PERFORMANCE

Although many benzodiazepines are generally well-tolerated, with higher doses they impair concentration and produce sedative effects even after their drug effects might be expected to have worn off (O'Hanlon 1985). The active effects of benzodiazepines may include sedation, depression, disorientation, daytime drowsiness, impaired balance, and with increased dosage they produce associated increased side effects. Although the margin of safety associated with these drugs is considerable overdose can occur, and continuous use for several months can result in psychological or physical dependence—that is, they can be addictive (Davis 1996). The effects of benzodiazepines are enhanced if accompanied by alcohol, and mixing some benzodiazepines with alcohol can have toxic effects (Carskadon 1993).

Medical providers who prescribe hypnotic medication for drivers must carefully weigh the potential risks of daytime impairment from a hypnotic medication against the benefit of obtaining a good night sleep. In reviewing the impairing effects of benzodiazepines on human performance, Wittenborn (1979) documented that the effects vary among the different types of benzodiazepines. When impairment was found, it was generally with higher doses, and within 2 to 6 h of drug administration. The effects were drug-specific, but there were observable impairments in the speed for accomplishment of simple repetitive acts, as well as impaired learning and immediate memory; however, overall, there was relatively little indication that well-established higher mental faculties are adversely involved. After that period the drug effects on behavior tended to dissipate (Wittenborn 1979). Koelega (1991) found that with young volunteers, vigilance is relatively sensitive to benzodiazepine impairment, causing individuals to miss more signals and respond more slowly to signals they did see. Kunsman et al. (1992) found that benzodiazepines at therapeutic doses when measured within 1 to 3 h of ingestion slowed simple and choice reaction time. However, continued repeated administrations eventually caused resistance (adaptation) to the impairing effects. Johnson and Chernik (1982) concurred with Wittenborn's findings, but also reported that high-dose levels of all benzodiazepines, taken at night, impair next-day performance, and the impairment is greater for long-life hypnotics.

An array of laboratory tests that relate to driving skills sensitive to sedation have been developed in various laboratories; however, the predictive validity of many of the lab tests tends to be unreliable. The most useful example of such test protocols is that of James O'Hanlon and colleagues in the Netherlands. In a decade-long series of driving studies, O'Hanlon developed an over-the-road driving test in which participants operate an instrumented vehicle over a 100 km primary highway circuit in normal traffic (O'Hanlon and DeGier 1986). Driver performance measures of speed and lateral position are recorded, and the standard deviation of the lateral position (SDLP) is most often cited as the primary outcome variable: the "weaving index" (O'Hanlon and Volkerts 1986; DeGier 2005).

O'Hanlon and his research team published more than 75 major studies about the effects of drugs on driving performance. In many of O'Hanlon et al.'s experiments, hypnotic drugs were taken by subjects for several nights before they were tested in actual driving tasks (O'Hanlon 1985; O'Hanlon et al. 1995). Almost all of the experiments employed the basic paradigm using an actual road driving course and reported SDLP as the principal indicator of driving performance.

All of the mean performance changes (degradations) occurring after two nights of drug treatment with benzodiazepines were significant in morning or afternoon tests, or both, except those following nitrazepam (5 mg) and temazepam (20 mg). The magnitudes of some changes were relatively small for lorazepam (1 mg), nitrazepam (10 mg), zoplicone (7.5 mg), and flunitrazepam (2 mg). These were the equivalent to the amount of impairment attributable to blood alcohol

concentrations in a range from just under 0.5 mg/mL to about 0.6 mg/mL. Slightly greater impairment was measured with 15 mg of flurazepam in the morning test. However, a serious degree of impairment, greater than the equivalent of a BAC of 1 mg/mL, was attributable to the residual effects of secobarbital (200 mg), flurazepam (30 mg), and loprazolam (2 mg) (O'Hanlon 1985). After a week of taking diazepam (5 mg, 3 times per day) and lorazepam (2 mg, twice per day) driving performance was impaired more than it was by a BAC of 1 mg/mL (O'Hanlon et al. 1995). Some of these results are depicted in Figure 1, along with results from subsequent studies undertaken by O'Hanlon and his colleagues.

Extracting the findings of many of those studies for a meta-analysis of the work, DeGier (2005) provided an informative figure summarizing the results in terms of *residual sedation* after sleep at measurement times ranging from 5 to 17 h post-dosing with various hypnotic drugs (mostly benzodiazepines and the so-called nonbenzodiazepines). DeGier's figure (Figure 1) is attributed to E. R. Volkerts (DeGier 2005).

The difference in SDLP relative to placebo is presented with an indication for comparison with calibrated BAC levels of 0.5, 0.8, and 1.0 (the horizontal lines across the figure). DeGier cites the comparison figure to illustrate two things: (1) that many prescribed hypnotics have a detrimental effect on driving (sleep–inertia hangover effects) even in the afternoon of the day following administration of the sleep-inducing dosing the night before; and (2) that some other hypnotics apparently do not have such effects, or at least they are substantially less. DeGier suggests that performance data such as those in his report (depicted in the figure) can assist prescribing health care providers and dispensing pharmacists in their decision making, making it possible for them to offer relatively safer alternative sleep-inducers to patients who drive and need hypnotic medications (DeGier 2005).

DeGier and Volkert's figure indicates that 6 of 11 hypnotics (mostly shown on the left in the figure) appear to impair driving performance less, in both the morning and the afternoon of the next day (after dosing) than do the other 5 hypnotic drugs (mostly depicted on the right side of the figure). The six drugs presenting lower sleep inertia were zaleplon, zolpidem, nitrazepam, lormetazepam, temazepam, and loprazolam, whereas the five hypnotics that produced higher sleep inertia scores the next day were flunitrazepam, zopiclone, secobarbital, oxazepam, and flurazepam (see also O'Hanlon 1985).

In another review, Berghaus and Grass (1997) summarized more than 500 experimental studies describing performance impairment on driving-related psychomotor and perceptual tasks as attributed to benzodiazepines. They reported a near-linear relationship between serum concentration and the percent of studies that obtained a significant effect, for both the short-acting triazolam and for the long-acting nitrazepam. Similar relationships were assessed for other benzodiazepines such as temazepam, flunitrazepam, flurazepam, alprazolam, bromazepam, diazepam, oxazepam, and lorazepam. When measured during the absorption phase (>3 h after administration), the impairment was about 30% higher than when it was measured during the elimination phase (>5 h). This effect is similar to that obtained for alcohol, but it is much stronger for benzodiazepines. Despite significant differences among individual benzodiazepines, as a class these drugs generally

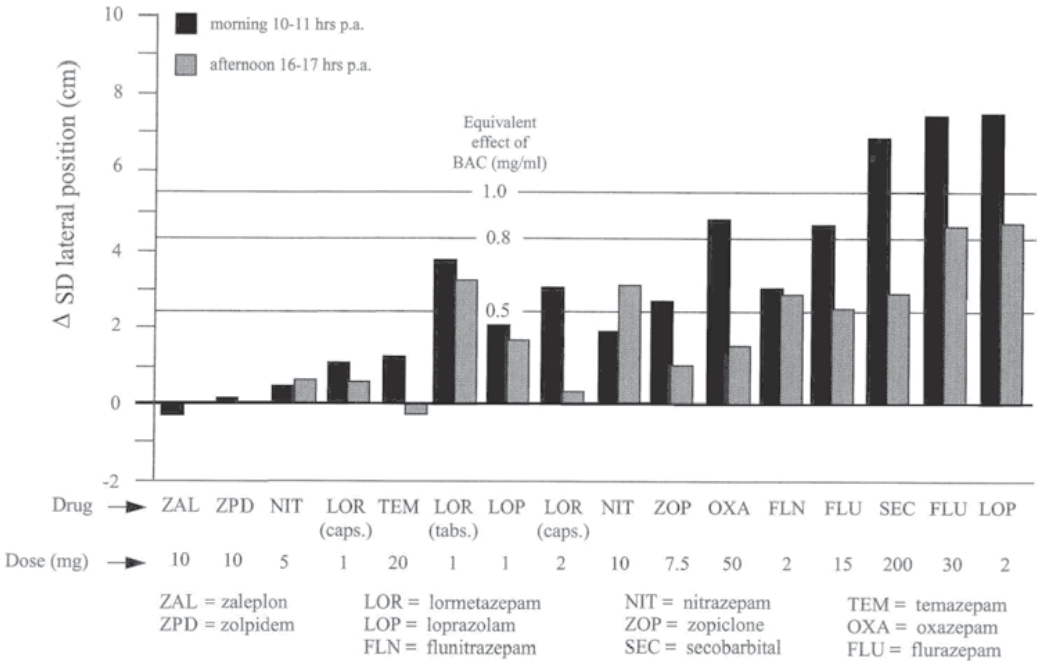

FIGURE 1 Residual effects of various hypnotics on Standard Deviation of Lateral Position (SDLP) while driving. Attributed to E. R. Volkerts, cited by DeGier (2005).

impair performance on most performance tasks—in particular, benzodiazepines impair performance on tasks that entail visual encoding of information (such as attention, vigilance, visual search, peak saccadic velocity, and critical flicker fusion) and on a variety of short-term memory tasks.

One study of drivers of commercial vehicles identified increased self-reported crash risk. Self-reported crash data were analyzed for Australian truck drivers who regularly or occasionally reported use of a variety of medications, including benzodiazepines. Drivers reporting the use of benzodiazepines were deemed to be 1.91 times more likely to have had a crash in the previous three years. This is compared with those who used antihistamines, who were 3.44 times more likely to have crashed; those who used narcotic analgesics, who were 2.4 times more likely to have crashed; and those with regular consumption of alcohol drinks, who were 1.09 times more likely to crash. Those who consumed mild stimulant drugs such as caffeine were no more or less likely to have crashed (Howard et al. 2004). [See also the assessment of various sleep-inducing drugs and the incidence of accident crashes by Gustavsen et al. (2008).]

In terms of practical operational use, military forces in several westernized countries have used fast-acting benzodiazepines [e.g., triazolam (Halcion®) or temazapam (Restoril®)] as hypnotics or as sedative sleep aids to help "put one to sleep quickly" (Nicholson et al. 1980, 1985; Penetar et al. 1989; Nicholson 1990, 1998, 2009; Wesensten et al. 1996; Caldwell et al. 2003). In such applications there is less concern over the immediate effects of the drugs on other forms of performance, because the person in a nap-induced state is "supposed to be sleeping." However, even though the U.S. Army continues to authorize limited use of triazolam for pre-deployment rest or for gaining sleep during continuous operations, it is now rarely prescribed (Caldwell et al. 2009). The U.S. military had concerns about individuals who upon awakening from benzodiazepine-induced sleep experienced hangover effects of antegrade short-term memory loss for events/information occurring before going to sleep (Penetar et al. 1989; IOM 1997). Consequently, the U.S. military has mostly moved on from employing the quick-acting benzodiazepines, switching instead to the use of less risky compounds such as administering synthetic forms of the hormone melatonin for use as sleep aids (Caldwell and Caldwell 2003, 2005; Caldwell et al. 2009). More recently, U.S. military forces also have been employing several newer sleep-promoting nonbenzodiazepine compounds such as zolpidem (Ambien®) and zaleplon (Sonata®) for quick acting sleep initiation (Caldwell et al. 2009; Gore et al. 2010).

As DeGier (2005) and the ICADTS Working Group pointed out, some of the new short-acting hypnotics could possibly serve as viable treatments for insomnia with commercial drivers. The FMCSA has published medical guidance regarding use of hypnotics in drivers of commercial vehicles since publication of the Psychiatry Medical Conference report in 1991 (FHWA 1991). This was reinforced in the most recent Psychiatry Evidence Report (Tragear et al. 2008), and the Medical Expert Panel recommendations (Metzner et al. 2009). These documents are advisory in nature, and recommended against commercial driver medical certification in drivers taking both benzodiazepine and nonbenzodiazepine hypnotics and anxiolytics. The bases of these recommendations are the multiple studies indicating impairment of cognitive function and driving ability for up to three weeks (DeGier et al. 1981; O'Hanlon et al. 1995; van Laar and Volkerts 1998; van Laar et al. 1992), and the increased odds of crash of 1.3 to 2.2 times greater than those individuals who did not use benzodiazepines. Crash risk was particularly increased in individuals of more than 40 years of age, and in the first week after prescription. The FMCSA noted that it "considers evidence, expert recommendations and other data, however all proposed changes to current standards and guidance will be subject to public notice-and-comment" (FMCSA Medical Expert Panel reports web page, accessed May 16, 2010).

Assessment of benzodiazepines. Use of benzodiazepines for induction of sleep, even for treatment of insomnia, has become less common with the recent entry of the alternative nonbenzodiazepines into the pharmaceutical marketplace. The several research studies examined and cited earlier provide sufficient indication that there would be some value in conducting additional, controlled, medical, and performance research to examine the potential of applications of some of the newer short-acting, and short-half-life hypnotics. Just as they might provide assistance in aviation operations (Caldwell et al. 2009; Caldwell 2011), potentially some of these newer hypnotics could be prescribed in safe sleeping environments when it is anticipated that commercial drivers have plenty of sleep time and recovery time before returning to their driving chores.

ALTERNATIVE SLEEP-INDUCING COMPOUNDS

There are a few additional chemical compounds that are being used or could be used to help induce sleep, but that do not fit conveniently into the two categories described previously. These are outlined here.

Alterial™

Alterial is an OTC, all-natural sleep inducer, which claims to help people fall asleep fast, stay asleep longer, and improve the quality of sleep all night long. Advertising claims report that Alterial contains natural ingredients (including melatonin, L-tryptophan, and valerian, along with additional ingredients) that help calm, relax, and prepare one for a good night's sleep. The claims are that Alterial does not leave a person feeling groggy and irritable the next morning, but rather energized, refreshed, and ready to perform. The manufacturer's claim is that the mix of ingredients helps a person achieve deep, restful sleep without dependency or side effects.

Assessment of Alterial. No research on Alterial™ and human performance measurement was located for this review; therefore, it is too early to make any predictive statements about this developmental compound.

Melatonin

Melatonin, a hormone secreted by the pineal gland in response to the onset of darkness, is believed to play a role in making us sleepy. Consequently, melatonin frequently has been referred to as our body's natural sleeping pill (Reiter and Robinson 1995). The benefits of both natural secretions of melatonin and applications of synthetic melatonin (available in pill or tablet form in health food stores) elicit interest in this synthesis because of the role melatonin plays in offering good potential to help people to feel drowsy, fall asleep, deal with insomnia, sleep better, and assist in re-setting an individual's circadian clocks during work shift changes (i.e., coping with work shift lag). For more than a decade synthetic melatonin has commonly been used for that purpose by some commercial drivers (Krueger 1996–2006). It has also been widely used in other transportation applications to help travelers to combat jet lag when making transmeridian flights (Petrie et al. 1989; Lieberman and Mays 1994). Accordingly, the coverage of this compound is more extensive here than that provided for other sleep promotion compounds.

The ways in which melatonin might alter sleep still are not well-understood, and medical researchers do not agree on exactly how melatonin helps people sleep. The internal core body temperature of humans has a distinct circadian rhythm, rising during the day and falling at night (a swing of only about a degree Fahrenheit) and having a strong influence on sleep. In general, it is easier to fall asleep when body temperature is falling, and it is easier to wake up or maintain wakefulness when body temperature is on the rise. Melatonin's effect on body temperature is one of the keys to its ability to enhance sleep. Melatonin is naturally synthesized in the pineal gland (a pea-size structure in the center of the brain) during the dark phase of the daily light/dark cycle and thus it is intimately tied into our circadian rhythm physiology (Comperatore and Krueger 1990).

As the sun sets each day and darkness begins, our internal core temperature starts to drop and the pineal gland produces a surge of a small quantity of melatonin (maintained at about a 0.3 mg level) that goes to all parts of the body. The nightly fall in body temperature happens to coincide with the steepest rise in nightly melatonin levels, which for adults takes place somewhere between 9 p.m. and midnight, depending on one's unique circadian rhythm (Campbell and Broughton 1994; Reiter and Robinson 1995). Melatonin levels are maintained in the human body during nighttime sleep (i.e., during darkness). The next morning, when sunlight hits the retina of the eyes, neural impulses signal the pineal gland to slow, and eventually cease melatonin production and, in daylight, the nighttime levels of melatonin already in the body quickly dissipate. As the foregoing indicates, it is important to take melatonin at the correct hour on the circadian physiological clock and to limit the amount of ambient light in the sleeping environment. Melatonin users are encouraged to give proper consideration to the timing of the onset of drowsiness and a strong urge to sleep.

It has been hypothesized by Mendelson (2005) that melatonin and its agonists might act to affect circadian systems through effects on melatonin receptors in the SCN (the site of the so-called circadian timing system). From his studies on animals, Mendelson speculated that one possibility is that the effects in humans are GABAergic, and the site of melatonin action may be similar to that of benzodiazepines, barbiturates, adenosine, and ethanol (Mendelson 2005). [For a review of early research on melatonin and sleep see Dawson and Encel (1993), and Cramer et al. (1974), who more than 35 years ago concluded that "melatonin induced sleep, behaviorally as well as by its polygraphic pattern, strikingly resembles natural sleep."] Subsequent studies repeatedly support this finding. Exogenously administered synthetic melatonin has been shown to induce a slowing of the electroencephalogram (EEG) to bring about sleep (Anton-Fay 1971, 1974; Cramer 1980).

Sack et al. (2003a, b) labeled synthetic melatonin as one of a new class of medicinal chemicals called chronobiotics because they are useful in adjusting the timing of circadian rhythms, capable of "resetting the biological clock," and therefore useful for dealing with jet lag, advanced and delayed sleep-phase patterns, and for treatment of other forms of insomnia. Sack and colleagues (Sack et al. 2003a), as well as others (Santhi et al. 2008), declared melatonin use to be safe, and, as a naturally occurring hormone, its administration causes fewer problems than many other "synthetic hypnotics." Taking synthetic melatonin seemingly has none of the negative side effects associated with traditional sleep medications. It does not significantly disrupt the sleep architecture. Individuals who take melatonin report sound nighttime sleep and no resultant grogginess the next day, nor does melatonin interfere with a person's memory or performance the next day as some other sleep aids do (Sack et al. 2003a; Santhi et al. 2008).

Researchers studying melatonin have searched for classical problems normally associated with traditional sleeping pills (e.g., suppression of REM sleep, losing the hypnotic impact over time with repeated use, and chance for addiction). Melatonin exhibited no substantial concerns on these topics. After numerous studies administering high doses of synthetic melatonin (10 to 100 mg) Wurtman and colleagues at the Massachusetts Institute of Technology demonstrated that 1.0 mg, 0.3 mg, and even as little as 0.1 mg of melatonin can hasten the onset of sleep, whatever the time of day (Lieberman et al. 1984; Zhdanova et al. 1995).

Hughes and Badia (1997) conducted a study examining the ability of melatonin in doses ranging from 1 to 40 mg to

induce naps, followed shortly after awakening 4-h post-dose, by administering tests of performance, memory, and fatigue. They found no carry-over fatigue and no negative effects on memory or performance. Even high doses of synthetic melatonin (50 mg) showed no interference with elderly adults (average age 84.5 years, who likely have no naturally occurring melatonin owing to old age) on memory, concentration, or motor control (Singer et al. 1994). This is quite different from what would happen with most, if not all, benzodiazepines.

Today, researchers generally induce sleep in their lab studies with considerably lower doses of from 0.1 to 0.3 mg of melatonin. It is important to note this because most synthetic preparations of melatonin sold in health food stores provide tablets ranging from 1 to 5 mg each, without specifying how much melatonin is actually in the tablets (quantity and quality assurance in such formulations is unspecified).

Benzodiazepines can become less effective after only two or three nights of use. By contrast, melatonin does not lose its effectiveness over time, and may even become more effective with chronic use as a sleep aid. In a study described by Reiter and Robinson (1995) 2-mg doses of melatonin were given to elderly volunteers for two months, and at the end of the treatment period, the participants fell asleep even more quickly than they did after the first week of treatment.

At the Walter Reed Army Institute of Research, Wesensten et al. (2005a) set out to determine whether combining melatonin with low-dose zolpidem might promote daytime sleep without exacerbating performance impairments seen with high-dose zolpidem alone. This research was initiated out of concern that at effective (higher) doses zolpidem not only induces sleep, but also impairs performance. They found no advantages to administering melatonin plus zolpidem "cocktails." Unlike zolpidem, melatonin alone (5 mg) improved daytime sleep without impairing memory and vigilance (Wesensten et al. 2005a).

Driver Applications of Melatonin

Experiments show that bright lights can trigger the response to cease a person's melatonin production even at night—an intervention that has been successfully tried to keep individuals alert in night-shift factory work (Santhi et al. 2008). Research findings are less clear about our body's ability to initiate production of melatonin simply by going into a darkened environment during daytime. However, a low dose of synthetic melatonin can be used to "trick" the body into thinking that dusk (darkness) has arrived earlier, especially if one enters a darkened room to attempt to sleep (Santhi et al. 2008). This has obvious implications for commercial drivers whose work and rest schedules are subject to frequent time-of-day changes (shift workers). Climbing into a darkened truck sleeper berth after taking synthetic melatonin is a napping strategy commonly advocated and used by commercial drivers (G. P. Krueger, personal communications with CMV drivers while teaching a decade of driver fatigue management classes, 1996 through 2006).

Military medical research illustrated that using synthetic melatonin as a sleep aid can be an important contributor to the repertoire of soldier fatigue countermeasures during military training and operations. O'Neill et al. (1996) addressed similar applications for use of melatonin, suggesting that it can be of assistance to commercial drivers attempting to combat fatigue. They suggested that melatonin would provide advantages both in terms of assisting drivers to obtain needed sleep during arduous work weeks and for use in adjusting to work schedule changes to combat work shift lag when their weekly schedules change (from night shifts to day shifts and vice versa). Practical applications taught to commercial drivers included ingesting synthetic melatonin and then attempting to obtain daytime sleep by using completely blacked-out sleeper berths in Class 8 trucks or in completely blacked-out hotel rooms during the day (Krueger and Brewster 2005).

Availability of Synthetic Melatonin

Synthesized into tablet forms, melatonin has been touted as one of the past decade's natural supplement "miracle compounds" and is sold in health food and grocery stores throughout the United States. Because melatonin is a synthesized hormone, in the United States at least, it is identified as a health food or dietary supplement and not as a drug. Therefore, synthetically produced melatonin is not subject to FDA approval. The FDA (www.fda.gov) merely states that melatonin is not a regulated compound, and that no FDA-sponsored evaluation and testing for safety, effectiveness, or purity has occurred. In some European countries, synthetic melatonin is classified as a neurohormone and it cannot be sold over the counter.

In the United States, synthetic melatonin is readily available in pill form and is inexpensive (a month's supply costs $12 to $20 at many health food stores). Because synthetic melatonin sold over the counter as a health food supplement is not governed by the FDA, its production is not required to adhere to "good manufacturing practices." Consumers are expected to trust what is on the label of the containers of melatonin sold in stores. Independent laboratory tests of popular synthetic melatonin products have on occasion found inconsistency regarding the amount of melatonin actually found in commercially sold products and what appeared as the contents on the container's labeling.

Ongoing medical research on melatonin continues to explore such questions as: What dosage and use regimen is safe for administration of synthetic melatonin for specific purposes? Most sleep research is done with doses of 0.1 and 0.3 mg of melatonin, and it would appear that less than a 1-mg dose is probably recommended for most operational applications. However, most readily available melatonin pills

or tablets may contain higher doses than the levels of melatonin normally secreted into the body by the pineal gland (0.3 mg at a semi-continuous level until daybreak). Many health food stores sell synthetic melatonin in 1 to 5 mg tablets—if those tablets were all melatonin, that would amount to a dose more than a 10 times higher than is seemingly required to induce sleep naturally, which may raise concerns about the advisability of repeatedly treating our bodies to this synthetic overdose of a hormone that is so intimately linked to many of our important biological processes. Although to date no significant hazardous concerns have arisen, in actuality not enough scientific data have been collected to identify supplier quality assurance issues and any potential long-term effects derived from chronically taking synthetic melatonin supplements.

Assessment of melatonin. Synthetic melatonin has been demonstrated to be beneficial to some individuals some of the time in assisting them to fall asleep, especially at times of day that are not normally conducive to sleeping (e.g., daytime circadian high points). It is essential that with its use additional steps are taken to ensure a darkened sleeping environment. Melatonin offers promise as a sleep-inducing aid for commercial drivers, especially for their use as an aid to induce naps during the daytime. Importantly, this topic suggests that some additional research may be needed to work out "sleep and alertness management protocols and fatigue countermeasures" for proper and appropriate use of synthetic melatonin in the particular work settings of commercial drivers. What is needed is to determine "treatment protocols," to develop "guidance" for *how* and *when* to use melatonin for help in inducing sleep; for example, for naps. Such protocols might be developed in conjunction with additional guidance about the use of other sleep-promoting compounds that may be suitable for truck, bus, and motorcoach drivers to use both at home and during operations on the road. Researchers could be asked to provide such guidance, perhaps ultimately promulgating it in the form of a user-friendly handbook.

Additionally, because synthetic melatonin marketed in health food stores and elsewhere is not governed by the good manufacturing practices act, some way must be determined to ensure that those who produce or supply the product provide sufficient quality assurance and indicate appropriate dose levels for the intended purposes of the commercial driver.

Alcohol Used as a Sleep-Inducing Aid

Perhaps the most commonly used technique for inducing sleep or for resolving insomnia is to drink modest amounts of alcohol (ethanol); perhaps a glass of wine or one or two beers before bedtime at night to relax and prepare to fall asleep. Reiter and Robinson (1995) estimated that 20% of insomniacs rely on alcohol to relax their muscles, ease their anxiety, and help them fall asleep. A telephone survey of approximately 1,000 representative adults in the general population reported that 10% had "self-medicated" with alcohol in the previous year (National Sleep Foundation 1998). A survey in Detroit, Michigan, reported that in the previous year, 13% had used alcohol to aid sleep, 18% used medication (either prescription or over the counter), and 5% had taken both (Johnson et al. 1998).

Although drinking alcohol has some sleep-inducing properties, using it to help one to fall asleep often promotes sleep disturbance as the night progresses (Mendelson 1987, 2005). Although a "nightcap" drink may help a person fall asleep more quickly, several hours later, as the alcohol oxidizes in the body, the sedative effect of the alcohol wears off and the alcohol may cause a rebound effect, making the person restless and agitated. In the second half of the night alcohol may disrupt dreaming (REM) sleep, thus making the period of sleep less restful and restorative of alertness. In that sense, alcohol is not a very effective sleep sedative.

Drinking a larger amount of alcohol before bedtime may also result in "hangover effects" the next morning, presenting symptoms of headache, grogginess, sleep inertia, and decreased alertness. Frequent consumption of alcohol is known to expose individuals to the risk of ethanol dependence or addiction. Alcohol has also been demonstrated to interact significantly in individuals with obstructive sleep apnea, making the condition worse by increasing the number of apneic episodes and causing deeper (worse) oxygen deprivation during sleep (Mendelson 2005).

Standard restrictions for commercial driving are that BAC cannot exceed 0.04%. Since 1995, the FAA also set the limits for pilots in the U.S. aviation industry at BAC of less than 0.04%, whereas the NTSB requires reporting any ethanol value exceeding a BAC equal to 0.02%.

Assessment of alcohol as a sleep aid. Although much information about the effects of alcohol on performance and health is known, consuming alcohol as a sleep inducer may result in disrupted and less restorative sleep, as the alcohol oxidizes over the several hours a person may be sleeping and therefore is not widely promulgated as a tenet of sleep maintenance guidance. The commercial driving community would benefit from development of user-friendly information and guidance documents on numerous chemical substances, including the use of alcohol as a sleep aid.

First-Generation Antihistamines Used as Sleep Aids

Millions of Americans experience problems with seasonal allergies, including sneezing and runny nose associated with the common cold, as well as allergic rhinitis; itchy, watery eyes; and itchy throat (i.e., bodily response to pollens in the air). For decades, the most common, effective treatment for such allergies has been to take so-called *first-generation antihistamines* of the diphenhydramine–hydrochloride type (which contain active ingredients of either diphenhydramine

or doxylamine) to block H1 receptors and therefore counter the actions of histamine, a naturally occurring chemical in the body (Kay et al. 1997; Kay 2000). Diphenhydramine is often used to treat the common cold, suppress coughs, and treat motion sickness (e.g., in Dramamine®), and for reactions to insect bites, hives, and rashes. First-generation antihistamines also produce mild to moderate sedative effects that cause drowsiness and sedation. A large segment of the sleep-deprived population occasionally turns to such first-generation antihistamines (with diphenhydramine) for assistance in falling asleep, and it is this feature that is of principal interest in this synthesis report.

The concern for transportation safety is two-fold: (1) that drivers who regularly take first-generation antihistamines for allergy relief may encounter performance impairments while driving a vehicle, owing to the drowsiness effects of maintenance levels of diphenhydramine in the body; and (2) occasionally taking first-generation antihistamines expressly for its sleep-promoting characteristics may leave one with next-day sleep inertia hangover effects on performance, and these may impact driving safety.

The FMCSA has provided advisory guidance on use of first-generation antihistamines in the Neurology Medical Conference Report (FHWA 1988), and the Pulmonary Medical Conference report (Turino et al. 1991), where use of first-generation antihistamines is not recommended. A more recent Pulmonary Evidence review and Medical Expert Panel report had not been published at the time of this writing.

The most widely known, first-generation antihistamine is Benadryl®—an OTC medication containing diphenhydramine, and that offers allergy relief. Allergy sufferers also commonly take chlorpheniramine, hydroxyzine, brompheniramine, promethazine, or doxylamine, along with other first-generation antihistamines under such trade names as Unisom®, Sleepgels®, Dytuss®, and Dramamine®. All of them cross the blood–brain barrier to block cortical histamine receptors. Antihistamine products containing diphenhydramine are accompanied by caution warnings that they not be used when driving, operating machinery, or performing other hazardous activities, as they may cause dizziness or drowsiness. Users also are warned that consuming alcohol while taking diphenhydramine may increase drowsiness and dizziness.

Benadryl®, in several capsule forms, usually contains 25 mg of diphenhydramine. Recommended doses of diphenhydramine (e.g., Benadryl®) for treatment of allergies in adults is 25 to 50 mg every 6 to 8 h, not to exceed 50 to 100 mg every 4 to 6 h. If the intended purpose is sedation; that is, for treatment of occasional insomnia, then the first-generation antihistamines such as diphenhydramine may help a person to induce sleep. For example, when it is being used as a sleep aid, 50 mg diphenhydramine should be taken approximately 30 min before bedtime. Taking diphenhydramine while also taking other sleep medicines or alcohol is not recommended, as these drugs interact in the body. First generation antihistamines are not recommended for chronic use, especially for those individuals with glaucoma, peptic ulcer, bronchial asthma, seizures, or prostate enlargement (Reiter and Robinson 1995).

Many other commercially available OTC sleep aids (e.g., Compoz, Nytol, Sleep-Exe, and Somnitabs) contain antihistamine as the active ingredient—most often as diphenhydramine. However, to be truly effective as sleep aids, many such antihistamine products would have to contain a higher dosage of diphenhydramine than what is normally inserted in each antihistamine pill or tablet by the manufacturers. Somnitabs®, for example, contain 25 mg of diphenhydramine per tablet. Some individuals in search of a suitable sleep aid take Dramamine, normally used for prevention and treatment of nausea, vomiting, or dizziness associated with motion sickness, because it contains 50 mg of diphenhydramine, which may relax them somewhat and help them to fall asleep.

The research literature on the use of antihistamines to induce sleep reports on several aspects related to operator performance. Kay et al. (1997) conducted a number of laboratory experiments demonstrating that first-generation histamine-1 receptor antagonists used to treat allergic disorders frequently cause sedation. Most sleep-inducing applications recommend that a person take first-generation antihistamine tablets at least 30 min to 1 h before the desired sleep period. Generally, these cause drowsiness and bring about reduced sleep onset latencies (versus placebo) anywhere from 1 to 8 h post-administration (Kay et al. 1997). However, some findings also indicate that first-generation antihistamines often can leave next-day drowsiness as a side effect (Mendelson 2005). For example, doxylamine has a half-life of 9 h, which means that if a person takes a doxylamine tablet at 2300 hours there will still be a significant amount in the bloodstream at 8 a.m. the next morning (Carskadon 1993). Tolerance to daytime sleepiness appears to develop rapidly, in approximately 4 days (Richardson et al. 2002). First-generation antihistamine preparations often are not potent enough to resolve serious sleep difficulties or nighttime anxiety. The major concern for using antihistamines for sleep management is over their potential for leaving aftereffects such as sleep inertia upon awakening.

If a person is using first-generation antihistamines for allergy relief (that is, he or she uses them not with intentions to aid in falling asleep per se, but rather to lessen allergic discomforts), it is critically important to note that bodily maintenance levels of all first-generation antihistamines, especially those containing diphenhydramine, have been demonstrated to diminish cognitive and psychomotor performance in healthy volunteers (Gengo and Gabos 1987; Gengo et al. 1989; Gengo and Manning 1990; Rice and Snyder 1993; Kay et al. 1997). Performance impairment may be of greater significance in patients when the allergic disorder per se adversely affects CNS function, as suggested in studies in which a reduction in cognitive functioning in patients was exacerbated by diphenhydramine (Gengo 1996). Laboratory

studies have shown diphenhydramine to decrease alertness, decrease reaction time, induce somnolence, impair concentration, impair time estimation, impair tracking, decrease learning ability, and impair attention and memory within the first 2 to 3 h post-dose (Moskowitz and Burns 1988; Gengo et al. 1989; Gengo and Manning 1990; Kay et al. 1997). Significant adverse effects on vigilance, divided attention, working memory, and psychomotor performance have been demonstrated. Impairment has been shown even in the absence of self-reported sleepiness or sedation. Sedative effects are dose-dependent. Interactions with alcohol can exacerbate performance decrements.

Diphenhydramine has repeatedly been shown to severely impair tracking and reaction time performance in actual on-the-road driving tests. Single doses of 50 mg have been shown to cause significant impairment during a 90 km highway test (measuring vehicle following constant speed and lateral position). In contrast, single 25- to 100-mg doses caused no significant driving effects during a short 15-min driving test. Using the Iowa Driving Simulator (passenger car), Weiler et al. (2000) compared the effects demonstrated by test participants who took only a single oral dose of 50 mg diphenhydramine with the effects corresponding to a blood alcohol concentration of 0.1 g/100 ml. Diphenhydramine caused significantly less coherence (ability to maintain a constant distance) and impaired lane keeping (steering instability and crossing the centerline) compared with alcohol. Overall driving performance was poorest after taking diphenhydramine, and participants were most drowsy after taking diphenhydramine (measured both before and after test driving). The authors concluded that diphenhydramine clearly impairs driving performance and may have an even greater impact than alcohol on the complex task of operating a motor vehicle (Weiler et al. 2000) [see also Betts et al. (1984)].

No reports were located documenting involvement of first-generation antihistamines in commercial driving studies, or as they might be implicated in actual crash fatalities. However, examination of more than ten years of pilot fatalities in U.S. general aviation crashes determined that approximately 5% were involved with antihistamines (Soper et al. 2000; Chaturvedi et al. 2005).

Assessment of first-generation antihistamines. Although first-generation antihistamines often provide effective treatment for allergy sufferers, such compounds frequently produce side effects such as drowsiness, sedation, fatigue, and an inability to concentrate (Gengo 1996). First-generation antihistamines (such as those containing diphenhydramine) were described with a particular focus on the notion that for some users such antihistamines also can bring about sedation when used for sleep promotion. However, the use of first-generation antihistamines is discouraged under task and work conditions that require the worker to maintain vigilance or to put forth sustained mental effort. Such cautions are issued because maintenance levels of all first-generation antihistamines have been demonstrated to have antagonist effects on cognitive performance and because in using them as sleep aids most have been demonstrated to leave a person with hangover inertia effects long after the sleep period has ended. Commercial drivers must be properly informed of the hazards and risks of using antihistamines both for allergy relief and for use as a sleep aid. Guidance information on this topic should be provided in materials prepared for overall information dissemination on chemical substances.

SUMMARY OF OPERATIONAL CONSEQUENCES OF SLEEP-PROMOTING COMPOUNDS

Table 2 summarizes the previous information regarding some key points of employing various sleep-promoting compounds in an operational setting, whether for commercial transportation purposes or some other work environment. The literature conveying U.S. military medical research findings and operational procedures being followed during training and military deployment activities is presented in Appendix B to this report.

SECOND-GENERATION NONSEDATING ANTIHISTAMINES FOR ALLERGIES

Second-generation antihistamines are described here to ensure that descriptions of both antihistamine types remain in close proximity in this synthesis report. Acute, seasonal allergic reactions may inhibit a worker's operational capability, which is of special concern during attention-demanding work; that is, commercial driving. A class of second-generation antihistamines (e.g., loratadine, fexofenadine, cetirizine, and astemizole)—the so-called nonsedating antihistamines—are touted to offer effective symptomatic relief for treating seasonal allergies. Allegedly, because they are said not to cross the blood–brain barrier, they should not bring about worker drowsiness and, therefore, should be more suitable to meet some CMV drivers' needs for allergy relief.

Second-generation antihistamines have improved safety profiles compared with the older first-generation antihistamines. This is because these second-generation agents have increased specificity for the H-1 receptor and bulky side chains that hinder their ability to cross the blood–brain barrier. As a result, second-generation antihistamines are more hydrophilic, having a higher affinity for peripheral histamine receptors than for cortical sites. Their active agents enter the CNS less readily, produce less sedation, and result in far less CNS impairment than do the first-generation antihistamines. Although second-generation antihistamines provide allergy relief, in principle they should not affect cognitive performance, making them a preferred treatment choice for many allergy sufferers (Kay et al. 1997; Timmerman 1999; Van Cauwenberge et al. 2000).

The FMCSA has provided guidance on "Non-sedating" or second-generation antihistamines in the Pulmonary Medical

TABLE 2
OPERATIONAL CONSEQUENCES OF SLEEP-PROMOTING COMPOUNDS

Benzodiazepines Rx	**Trade Name**	**Average Half-Life**	**Recommended Use**	**Comments/ Cautions**
Temazepam	Restoril®	8.0–12.0 hr	Daytime sleep; sleep maintenance	Need 8-hr sleep period post dose
Triazolam	Halcion®	2.0–4.0 hr		
Diazepam	Valium®			
Lorazepam	Ativan®			
Alprazolam	Xanax®			
Chlordiazeproxide	Librium®			
Clonazepam	Klonopin®			
Newer Hypnotics (Rx)				
(non-Benzodiazepines)			Sleep initiation; napping strategy	
Zolpidem	Ambien®, Stilnox®, Myslee®	2.0–2.5 hr	Sleep initiation; intermediate length naps	Promotes sleep of 4–7 hr
Zaleplon	Sonata®, Starnoc®	1.0 hr	Short naps; 20 mg for sleep initiation	w/20 mg, no hangover effects at 6+ hr
Eszopiclone	Lunesta®	5.0–6.0 hr	Sleep initiation, & maintenance	Minimal residual effects at 10 hr
Indiplon & Indiplon modified release		~ 1.5 hr	Sleep initiation & maintenance	Undergoing clinical trials
Ramelteon	Rozerem®		Sleep initiation, but not for sleep maintenance	Long-term treatment of insomnia
Alternative Sleep Inducers				
Alterial	Includes melatonin, L-tryptophan, valerian		All natural sleep inducer	Claims restful sleep with no residual effects
Melatonin	Synthetic hormone in health stores	Dissipates in blood stream in daylight	Effective daytime sleep inducer in darkened room	Works for some people; no side effects or hangover
First Generation Antihistamines	Benadryl®, Unisom®, Sleepgels®, Dytuss®, Dramamine®	Maintains in body for allergy relief	25–50 mg diphenhydramine induces sleepiness	Maintenance level may produce hangover sleepiness

Conference report (Turino et al. 1991), where use of these substances is allowed.

Gary Kay and his colleagues conducted laboratory experiments comparing the effects of first- with second-generation antihistamines. In a comprehensive review, Kay and colleagues reported impairments to cognitive performance attributable to second-generation nonsedating antihistamines that ranged from none to mild (Kay et al. 1997a, b; Kay 2000; Kay and Quig 2001). Although several comparison studies confirm the hypnotic effects of diphenhydramine, basically they showed no significant differences in sedation with some of the non-sedating second-generation antihistamines such as astemizole or loratadine (Roth et al. 1987; Schweitzer et al. 1994; Gengo and Gabos 1987).

In a comparison of effects of three different antihistamine drugs on driving, Ramaekers and O'Hanlon (1994) examined the effects of diphenhydramine, terfenadine (second-generation: Seldane), and acrivastine on driving performance as a function of dose and time after dosing. Lateral deviations (lane weaving and crossings) during driving were found to vary with both the particular drug chosen and with the dose administered. This prompted additional studies evaluating performance of subjects driving while using either first- or second-generation antihistamines (O'Hanlon and Ramaekers 1995; Ramaekers et al. 1995).

Single doses of diphenhydramine (50 mg), clemastine (2 mg), and multiple doses of triprolidine (5 and 10 mg) produced changes equivalent to those produced by BACs of 0.5 to 1 mg/ml. However, terfenadine (second-generation) was taken in single doses of up to 180 mg and multiple doses over 4 days of up to 120 mg twice per day. The single dose and multiple doses of 60 mg taken two times per day, and a 120-mg dose four times per day never produced a significant

rise in lateral position tracking (SDLP). On the contrary, there was a tendency for 60 and 120 mg to produce a slight fall in SDLP, suggesting a mild stimulating activity (or perhaps a performance settling effect) of the drug. When subjects took doses of 120 mg twice per day for 4 days, impairment was equivalent of up to that of 0.05% BAC (O'Hanlon and Ramaekers 1995). Only a few studies have reported some degradation of cognitive and psychomotor performance with second-generation antihistamines; see for example the study by Rice and Snyder (1993) on terfenadine: Seldane—which is no longer on the market; and see also studies here reporting on the performance effects of cetirizine (Zyrtec).

Several of the newer second-generation antihistamines are briefly described here.

Cetirizine

Although second-generation antihistamines are claimed by their pharmaceutical manufacturers to be nonsedating, research reports some second-generation antihistamines [e.g., cetirizine (Zyrtec)] do produce some level of cognitive impairment (Vacchiano et al. 2008). Cetirizine, which is demonstrated to be more sedating than the other nonsedating antihistamines, has been reported to impair cognitive performance in a number of studies (Ramaekers et al. 1992; Lockey et al. 1996; Meltzer et al. 1996; Nicholson and Turner 1998; Howarth et al. 1999). After investigating the effects of cetirizine on tasks such as tracking and vigilance as they relate to aviation personnel, Nicholson and Turner (1998) suggested that cetirizine should not be used by aviation personnel. Cetirizine's effects on SDLP in driving studies are a matter of contention between different groups of investigators (O'Hanlon and Ramaekers 1995). One showed a single-dose of cetirizine (10 mg) impaired, whereas another found no effect with that dose on either the first or fourth day. Cetirizine may be slightly sedating even at normally recommended doses.

In 2007, the FDA approved nonprescription use of Zyrtec-D (combining cetirizine with a nasal decongestant) for use in obtaining relief from hay fever or other upper respiratory allergies.

Fexofenadine

In a similar study, Nicholson et al. (2000) demonstrated that fexofenadine (Allegra®) had no impairing effects on tracking, vigilance, and other tasks related to aviation. Bower et al. (2003) and Vacchiano et al. (2008) demonstrated no significant effects of fexofenadine on a variety of cognitive performance tasks, concluding that fexofenadine is comparable to placebo in its effect on cognitive skills involving accuracy, speed, and attentiveness; each important for piloting an aircraft. The results were comparable to those involving fexofenadine in assessments of the types of cognitive performance expected in driving (Ramaekers et al. 1992; Hindmarch and Shamsi 1999; Hindmarch et al. 2002). Further evidence for the lack of cognitive decrements by fexofenadine was demonstrated in a study in the Iowa Driving Simulator that showed that fexofenadine subjects had better coherence (ability to maintain a constant distance from a lead car with randomly changing speed) compared with subjects with diphenhydramine. In addition, the ability to stay in the lane, measured by steering instability and crossing the centerline, was impaired in alcohol- and diphenhydramine-affected subjects, as compared with those with only fexofenadine (Weiler et al. 2000). Of the three most popular second-generation antihistamines, fexofenadine (Allegra®) appears to be the least sedating, even in higher doses.

Loratadine and Desloratadine

Loratadine and desloratadine (Claritin®, Claritin-RediTabs®, Alavert, and others) is a piperidine histamine H-1 receptor antagonist with anti-allergic properties and without sedative effects. In April 1993, the FDA approved loratadine as a second-generation antihistamine for use without a prescription. Loratadine is a longer-acting antihistamine that blocks the actions of histamine; it does not enter the brain through the blood, and it does not cause CNS effects. Loratadine is generally used for the relief of nasal and nonnasal symptoms of seasonal allergic rhinitis and to treat patients with chronic urticaria, a type of allergic skin rash. The distributor has indicated that there may be occasional side effects with loratadine, including headache, drowsiness, fatigue, and dry mouth.

Claritin-D® is a combination of loratadine and the decongestant pseudoephedrine (Geha and Meltzer 2001). Although potentially effective in providing relief of runny nose, sneezing, and nasal stuffiness from the common cold, it is also used for relief of nasal and nonnasal symptoms of various allergic conditions such as seasonal allergic rhinitis. Side effects of Claritin-D may include stimulation of the nervous system leading to nervousness, restlessness, excitability, dizziness, and headache. Loratadine (Claritin®) does bring about some sedation at higher doses and is less potent than fexofenadine (Allegra) and cetirizine (Zyrtec). Pseudoephedrine used as a decongestant can be associated with cardiac arrhythmia, hypertension, or other adverse effects in susceptible individuals.

A review by Kay and Harris (1999) revealed minimal effects of loratadine on sedation, cognition, mood, and psychomotor performance. Satish et al. (2004) suggested seasonal allergic rhinitis (SAR) by itself diminishes task performance and decreases quality of life. These experimenters administered desloratadine to a group of subjects who were experiencing SAR, and gave a placebo to another group. Their performance was measured on simulated real-world information processing scenarios, which ranged through several levels of difficulty from easy to difficult decision-making tasks. Desloratadine

either completely restored performance to the level of the asymptomatic placebo control or improved performance in six of nine performance categories, which previously had been diminished by the presence of SAR. Their findings suggested that treatment with desloratadine has beneficial effects on workplace performance when individuals suffer from SAR (Satish et al. 2004).

In the car driving experiment reported by O'Hanlon and Ramaekers (1995) and briefly described earlier, loratadine in single doses of 10 and 20 mg produced no significant rise in SDLP (lane weaving). When given in 20-mg doses four times per day for 4 days, the impairment attributable to loratadine was similar to that of terfenadine. Building on that study, Vuuman et al. (2004) compared the acute effects of desloratadine with diphenhydramine (active control) and placebo on performance of healthy subjects evaluated with standard over-the-road driving tests, and also on a battery of conventional performance tests. The subjects were given either a single dose of 5 mg of desloratadine, 50 mg of diphenhydramine, or placebo during each period of a randomized, double-blind, three-way crossover study. Two hours postdosing subjects operated a specially instrumented vehicle in a 90-min test designed to measure their ability to (1) maintain constant speed and lateral position while following another vehicle at a constant distance, and (2) respond to brake signals. Additional test batteries were administered. No significant differences were noted between desloratadine and placebo on SDLP, whereas diphenhydramine significantly increased SDLP. Brake reaction time was significantly faster following treatment with desloratadine than diphenhydramine. No differences were seen among treatments in deviation of speed or distance to the lead car. The majority of performance tests showed no significant differences among groups. Vuuman et al. (2004) concluded that desloratadine at a therapeutic dose does not impair driving performance.

In a study combining alcohol and desloratadine (7.5 mg daily), Scharf and Berkowitz (2007) demonstrated that a single dose of desloratadine does not potentiate alcohol-mediated CNS impairment, and desloratadine alone or in combination with alcohol was safe and well-tolerated. Nicholson et al. (2003) did a study examining effects of desloratadine on performance and sleepiness and concluded that 5 mg of desloratadine appears to be free of adverse effects on psychomotor performance, daytime sleep latencies, and subjective sleepiness, and could prove to be suitable for those working in skilled activity including transportation.

Assessment of antihistamines. It is the intent here to cull through the results of available research studies and to report on those that depict the effects of various chemical compounds. It is not within the scope of this synthesis to propose "treatment protocols" regarding whether antihistamines could or should be used by commercial drivers, nor to be specific about when one should consider taking a particular antihistamine. Because so many commercial drivers experience seasonal discomfort attributable to allergies, rhinitis, and other ailments treatable with antihistamines, more performance-oriented research should be done with second-generation, and eventually third-generation antihistamines to determine their potential efficacy for allergy treatment (relief), without producing degrading sedation effects on driving alertness, fatigue, and performance.

Based on subsequent research results, what is needed is to (1) provide summary information to commercial drivers and their employers about what these new second-generation antihistamines are about, (2) spell out their advantages and disadvantages, and (3) begin to propose such guidance in an easy-to-relate-to format that describes their probable safe application for drivers who require seasonal allergy relief several times per year.

CHAPTER FOUR

STIMULANTS AND ALERTNESS-ENHANCING COMPOUNDS

INTRODUCTION TO STIMULANTS AND ALERTNESS-ENHANCING COMPOUNDS

Many commercial drivers put in long hours of driving on a daily basis (11 h permitted out of a 14-h work day). Their situation presents a particularly acute safety concern in that they might develop driver fatigue during long drives common in over-the-road operations. Drivers in short-haul operations may alternate lengthy duty periods, waiting to pick up or deliver loads locally, or make multiple revenue run deliveries stretching their duty day. In this synthesis the safety concern turns attention to the possibility of some commercial drivers using wake-promoting compounds (stimulants) in their attempts to maintain alertness and to sustain or enhance driving performance. Discussion focuses on stimulating and wake-promoting compounds often mentioned in the commercial driving community and devotes special attention to the effects on driving safety.

> *Caveat.* A word of caution, although some of the advantages and disadvantages of medical management of prescription stimulant use are described, it is not the intent to suggest that stimulants of any type can be a replacement for commercial drivers adhering to a personal good sleep management program. Obtaining a sufficient *quantity of quality sleep* on a daily basis is the most conducive way to maintain alertness and to manage driver fatigue. Sleep also is an important key to maintaining overall good health (Krueger 1989; Krueger et al. 2007a, b).

STIMULANTS AND ALERTNESS-ENHANCING COMPOUNDS

A variety of "wake-promoting" chemical compounds, referred to as stimulants, include not only those in the Schedule II drug category, such as amphetamine-like compounds, but also include the two most common and less threatening stimulants: caffeine and nicotine. Some stimulant drugs have a role in the clinical treatment of conditions such as excessive sleepiness attributable to sleep disorders (e.g., narcolepsy), ADHD, and depression (Mitler and O'Malley 2005; Kay et al. 2009). Because their pharmacologic profiles are diverse, clinicians guide the selection of stimulating agents based on a variety of factors, including time of onset, length of activity, degree of tolerance in chronic use, side effects expected, abuse liability, and, importantly, a knowledge of whether and how the use of such medication might affect a person's job performance.

Wake-promoting medications fall into three chemical classes: (1) direct-acting sympathomimetics, such as the alpha-adrenergic agonist phenylephrine; (2) indirect-acting sympathomimetics, such as amphetamines, methylphenidate (e.g., Ritalin®), mazindol, and pemoline; and (3) the "non-stimulants" that are not sympathomimetics, which have different mechanisms of action, such as modafinil and caffeine (Mitler and O'Malley 2005). The pharmacology of sympathomimetics is reviewed by Nishino and Mignot (2005).

Prescription Stimulants and Amphetamines

Introduction

The most potent stimulant of natural origin, cocaine, has medicinal uses; however, for the most part, its current use is illicit. Research literature on cocaine and on marijuana (cannabis, another substance illegal in many jurisdictions) and their effects on driving performance are briefly described together in Appendix A to this synthesis report. Legitimate prescription stimulants include amphetamines, methylphenidate, and others. Although there is a vast literature documenting research on most stimulants, the concern here is to describe those stimulants that hold some potential for practical use as alertness-enhancing compounds in transportation operations. For interested readers, a considerable number of such literature citations involving research on stimulants and performance are listed in the web-only Appendix E (Bibliography).

Amphetamine, Dextroamphetamine, and Methamphetamine

Amphetamines and related compounds may be prescribed to treat some medical conditions. Medical uses for amphetamines include the treatment of narcolepsy, attention deficit/ADHD, and treatment-resistant depression.

Amphetamines (with common street names such as uppers or speed) once were available over the counter. The three most common stimulant drugs amphetamine, dextroamphetamine, and methamphetamine are similar in their effects. In years past, many segments of the population, especially workers with extensive or irregular work hours, took amphetamines orally, often in excessive amounts. As with all stimulants, amphetamines can produce dependence and therefore as their use became commonplace they became identified as having a high abuse potential. A prescribed dose of

amphetamines for medical treatments has often been between 2.5 and 15 mg per day. Repeated drug users on a "speed binge" have been known to inject hundreds of times those amounts every 2 to 3 h (Davis 1996). OTC availability of such amphetamines was stopped in the United States in 1971 by the Controlled Substances Act when they became Schedule II drugs, and they are now legally obtainable only by prescription (Hart and Wallace 1975). However, illegal clandestine laboratories produce large amounts of amphetamines, particularly methamphetamines, for illegal distribution. The abuse potential of amphetamines has also led to a reduction in prescription issuance by physicians.

Military forces of several countries have expended considerable research effort in medical research labs examining the potential for the use of amphetamines in operational applications. For the sake of completeness in this synthesis a limited amount of the performance research done with several of the more prominent stimulants and amphetamines is briefly described in Appendixes A and B. Appendix B also lists details of the U.S. military's drug management protocol adhered to in the use of stimulants in operations and training.

Amphetamine assessment. The use of many stimulants such as amphetamines (with the exception of caffeine, nicotine, and perhaps modafinil/armodafinil) in any operational environment is inherently risky. [See for example the treatise on methamphetamine and driving behavior risks by Logan (1996, 2002).] Whereas use of amphetamines is not likely to become acceptable operational practice for ameliorating the effects of sleep loss or drowsy driving in drivers of commercial vehicles, urine drug testing and post-crash forensic analyses indicate that some commercial drivers do partake of amphetamines and other stimulants not usually recommended with intentions of driving.

Modafinil

Modafinil (ProVigil®), chemical name 2-diphenylmethylsulfinyl-acetamide, is a chemically unique, stimulant-like compound that was developed in France in the 1970s–80s (Nishino and Mignot 2005). Modafinil is a primary metabolite of adrafinil (Olmifon), a mild CNS-stimulant drug used in Europe to relieve excessive sleepiness and as a vigilance-promoting compound. Adrafinil is a prodrug, primarily metabolized in vivo to modafinil, resulting in nearly identical pharmacological effects; however, it has not been approved for use in the United States. In 2004, modafinil (as Provigil®) was approved by the FDA for treatment of narcolepsy, for SWSD, and for persistent and excessive daytime sleepiness associated with effectively treated obstructive sleep apnea. In some countries, modafinil is approved for idiopathic hypersomnia (all forms of excessive daytime sleepiness where causes cannot be established). In June 2007, the FDA also approved of a related compound: armodafinil (Nuvigil) as a stimulant-like drug for the treatment of narcolepsy and SWSD, and as an adjunctive treatment for obstructive sleep apnea. Importantly for our purposes here modafinil, adrafinil, and possibly armodafinil would appear to have some application for commercial drivers in maintaining alertness, even while driving.

In the United States, modafinil is classified as a stimulant, and as a nonnarcotic Schedule IV controlled substance. The use of modafinil therefore requires a prescription. Modafinil is available under the trade names ProVigil®, Vigil®, Alertec®, Modiodal®, and Modasomil®. As with other stimulants, modafinil increases the release of monoamines, but also elevates hypothalamic histamine levels, leading some researchers to consider modafinil a "wakefulness promoting agent" rather than a classic amphetamine-like stimulant. Lagarde and Batejat (1995) described modafinil as a "eugregoric," meaning "good arousal" (Lagarde et al. 1995). This unique class of eugregoric compounds contains only modafinil, its chemical precursor adrafinil (Milgram et al. 1999), and armodafinil, all three of which were developed as "wake promoting agents" to improve wakefulness. They are sometimes referred to as somnolytics (Mitler and O'Malley 2005).

As the primary metabolite of adrafinil, modafinil's activity is similar; however, adrafinil requires a higher dose to achieve equipotent effects. The basis of modafinil's uniqueness lies in its ability to stimulate only when stimulation is required; as a result, the "highs and lows" associated with other stimulants such as amphetamines are absent with eugregorics. The lows are sometimes referred to as "recovery sleep" and modafinil, unlike amphetamines, is said not to produce the need for this prolonged recovery, or "rebound hypersomnia." A totally unique feature of modafinil and adrafinil therefore is that a person wishing to remain awake can use either of them to do so with a far greater level of alertness, but at the same time the compounds will not prevent the person from sleeping if he or she wants to (Buguet et al. 1995; Grady et al. 2010).

Modafinil is thought to have less potential for abuse than other stimulants owing to the absence of any significant euphoric or pleasurable effects; therefore, it is thought to be nonaddictive. The central stimulating effect of modafinil shows dose and time-related features (McClellan and Spencer 1998; Nishino and Mignot 2005). Prescription single-dose levels of modafinil are normally between 100 and 400 mg taken orally. Based on their studies, Buguet et al. (2003) recommended 200 mg of modafinil for use in sustained operations. As with some other studies, they demonstrated that the 400-mg dose has not been shown to be more effective than a 200-mg dose. Modafinil achieves maximum levels in the blood between 2 to 4 h after administration, and its half-life ranges from approximately 10 to 15 h (Robertson and Hillreigel 2003). Modafinil exhibits maximum vigilance-enhancing properties, peaking 4 h after a dose of 200 mg. A participant can re-dose with 100 to 200 mg every 4 to 6 h. Occasional side effects such as headache can occur with 300 mg/day doses; and at higher doses (>800 mg) increased blood pressure and increased supine pulse, increased urination, palpitation, tachycardia, excitation, and aggressive tendencies may occur. There also

have been some reports of modafinil-inducing skin rashes; a small number of them severe enough to require hospitalization.

Since the mid-1980s, numerous clinical trials and studies confirmed the ability of modafinil and adrafinil to increase awakeness and alertness without the serious side effects of dependency. Studies during sleep deprivation found modafinil to be as effective as amphetamines and large doses of caffeine for maintaining vigilance, alertness, and cognitive performance with only minor side effects (Lagarde and Batejat 1995; Lagarde et al. 1995; Pigeau et al. 1995; Akerstedt and Ficca 1997; Baranski and Pigeau 1997; Baranski et al. 1998, 2004; Batejat and Lagarde 1999; Wesensten et al. 2002, 2004; Caldwell et al. 2004; Caldwell and Caldwell 2005). Walsh et al. (2004) demonstrated that the physiologic sleepiness and neurobehavioral deficits that occur during a typical night shift can be attenuated by modafinil. For them, 200 mg of modafinil also had beneficial effects on some measures of executive function (e.g., optimal telegram test involving verbal creative thinking, card sorting, and number sequencing).

Mitler and O'Malley (2005) described the research of the U.S. Modafinil in Shift Work Sleep Disorder Study Group, with its concern for shift workers who, like many commercial drivers, suffer at least transiently from effects of both sleep deprivation and circadian misalignment. A Harvard Medical School project enacted a double-blind, placebo-controlled, 3-month study of more than 200 night-shift workers (Czeisler et al. 2005). At baseline, the shift workers were pathologically sleepy, as their Multiple Sleep Latency Test (MSLT) fall asleep times were approximately 2 minutes, they demonstrated significant cognitive impairment (slower reaction times measured by a psychomotor vigilance task), and they exhibited numerous mistakes, near-misses, or accidents at work or while driving home after work. When workers took 200 mg of modafinil at the beginning of their night shift, all of these measures improved substantially. Furthermore, this treatment did not interfere with their ability to sleep during time off duty (Czeisler et al. 2005).

On the basis of this and other evidence, the FDA, in 2004, approved modafinil for treatment of excessive sleepiness resulting from SWSD. Together with a program of nonpharmacologic measures to protect sleep time and sleep ability in this shiftwork population, this represents a potentially lifesaving treatment for these adults (Mitler and O'Malley 2005). Subsequently, in June 2005, armodafinil (Nuvigil) was also approved by the FDA for treatment of SWSD. This research with modafinil and the subsequent FDA approval of its use for SWSD present distinct implications for practical applications as a fatigue countermeasure for commercial drivers whose shift-work schedules often are "nonstandard." Additional research is needed to determine appropriate protocols for the use of modafinil and/or armodafinil as potential alertness and fatigue management countermeasures for commercial drivers.

The first important study employing modafinil as a stimulant in humans was done by French military medical researchers (Lagarde and Batejat 1995; Lagarde et al. 1995; Batejat and Lagarde 1999), who found that 200-mg doses of modafinil every 8 h reduced episodes of microsleep and maintained more normal (i.e., rested) mental states and performance levels (measured through questionnaires, visual scales, and sleep latency tests) than placebo for 44 h of continuous wakefulness (but not for a full 60 h of sleep deprivation). The modafinil participants sustained a satisfactory level of vigilance with an absence of sleep episodes, unlike the placebo group that gradually declined and slipped into microsleep episodes as one might expect when remaining awake for longer than 24 h.

Since that time, military forces in France, the United Kingdom, and the United States have shown a particular interest in modafinil as an alternative for amphetamine—the drug traditionally employed in combat situations where troops face sleep deprivation during lengthy missions. Their respective medical research labs have done experiments on potential operational applications for modafinil. These studies showed that modafinil reduces degradation of cognitive performance, enhances vigilance, and promotes alertness and arousal during extended or sustained operations. It was claimed that modafinil "could keep an army on its feet and fighting for three days and nights with no major side-effects" (TTCP 2001).

Caldwell and colleagues (2000) found that 200 mg of modafinil every 4 h maintained simulator flight performance of military helicopter pilots at or near well-rested levels despite 40 h of continuous wakefulness; however, there were some complaints of nausea and vertigo (attributed to the high dose of modafinil used). In a subsequent flight simulator study with U.S. Air Force F-117 fighter jet pilots, three 100-mg doses of modafinil, administered every 5 h, sustained flight performance within 27% of baseline levels during the later part of a 37-h period of continuous wakefulness. Similar beneficial effects were seen on measures of alertness and cognitive performance (Caldwell et al. 2004, 2009). Furthermore, the lower dose of modafinil (100 mg) produced these positive effects without causing the side effects noted in the earlier study (Caldwell et al. 2000, 2009).

Caldwell and Caldwell (2005) and Caldwell et al. (2009) suggested that because these and similar studies found such positive results with modafinil, the eugregoric compound is gaining popularity in military communities as a way to enhance the alertness of sleepy personnel. Modafinil is considered safer and less addictive than the amphetamines; it produces less cardiovascular stimulation, has lower potential to exacerbate hypertension and cardiac arrhythmias than amphetamine; and, despite its half-life of approximately 12 to 15 h, the drug's impact on sleep architecture is minimal. Alternatively, other experimental data suggest that modafinil is less effective than amphetamine (Mitler and Aldrich 2000).

At the Walter Reed Army Institute of Research, Wesensten et al. (2002) tested modafinil in 50 healthy adults to determine whether it should replace caffeine for restoring performance

and alertness during 48 h of total sleep deprivation. They reported that performance and alertness were significantly improved by modafinil at 200 and 400 mg relative to placebo, and effects were comparable to those obtained with 600 mg of caffeine. There was a trend toward better performance at higher modafinil doses, suggesting a dose-dependent effect, but the differences between modafinil doses were not significant. Performance-enhancing effects were especially salient during the time frame of 6 a.m. through 10 a.m. They concluded that, as with caffeine, modafinil maintained performance and alertness during the early morning hours, when the combined effects of sleep loss and the circadian performance and alertness trough is usually manifest. Few instances of adverse subjective side effects (nausea, heart pounding, etc.) were reported (Wesensten et al. 2002).

Thus, equivalent performance- and alertness-enhancing effects were obtained with two drugs (caffeine and modafinil) possessing different mechanisms of action. Wesensten et al. (2002) also concluded that modafinil did not offer significant advantages over caffeine (which is more readily available and less expensive) for improving performance and alertness during sleep loss.

A later study at Walter Reed indicated that a single 400-mg dose of modafinil was as effective as 600 mg of caffeine or 20 mg of d-amphetamine for sustaining the simple psychomotor and cognitive performance of sleep-deprived volunteers for 12 h post-dose (Wesensten et al. 2004a, b). In terms of efficacy alone, these Walter Reed laboratory data suggest that modafinil effects are similar to those of high-dose caffeine and moderate amounts of dextroamphetamine. In a U.S. Air Force 88-h sleep loss study of simulated military ground operations, 400-mg doses of modafinil per day were mildly helpful at maintaining the alertness and performance of subjects compared with placebo; but the researchers concluded that this dose was not high enough to compensate for most of the effects of complete sleep loss (Whitmore et al. 2006).

A 3-year-long study involving chronic treatment with modafinil was conducted in Europe, where modafinil has been available with a prescription for more than two decades. That study determined that modafinil reduced drowsiness in 83% of hypersomniac patients and 71% of narcoleptics, and the prolonged use of modafinil for up to 3 years did not exhibit any systematic indication of related health risks (Baranski et al. 2001). Studies of modafinil that were carried on for longer than a month's duration indicated that modafinil may be effective in appetite suppression and therefore may offer some assistance in weight loss protocols. This topic also requires substantive research to delineate the factors associated with this variable.

Because of the importance of sleep disorders in the commercial driving community, it is worth mentioning that modafinil and armodafinil have been used to promote wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome (as an adjunct for treatment of the underlying obstruction), and SWSD. Bittencourt et al. (2008) reported on a placebo-controlled study employing modafinil with confirmed obstructive sleep apnea patients who also were on effective continuous positive airway pressure (CPAP) treatment. The study found that modafinil, used adjunctively with CPAP, reduced daytime subjective sleepiness in obstructive sleep apnea patients who regularly use CPAP. Although participants still experienced some sleepiness, modafinil helped improve objective measures of behavioral alertness and reduce functional impairments.

Assessment of modafinil. As laboratory research cited in this review indicates, modafinil offers many of the same stimulant benefits as caffeine and amphetamines, but with slightly different physiological side effects, some which are less offensive, such as not being as threatening to blood pressure as caffeine tends to be. Several of the studies demonstrated the utility of modafinil during circadian lulls of mid-afternoon and after midnight. Importantly, unlike any other stimulant (including caffeine), a person taking modafinil can still decide to go to sleep; that is, to "overrule the stimulating effects" and be able to take a nap without interference from the "drug" (Ballas et al. 2002). That feature can offer a real boost for commercial driving applications, and that aspect of modafinil could be explored in subsequent research programs looking for just such an application.

Studies as those described earlier have prompted a call for more research to determine the level of effectiveness of using modafinil in potential operational protocols with commercial vehicle drivers. Of the "newer chemical stimulants" being identified, modafinil (and chemically related compounds) may offer the most significant potential as an efficacious and safe chemical countermeasure to fatigue and could be of assistance to commercial drivers (even for chronic use) in the quest for alertness management in highway driving. In particular, additional research should help to develop a suitable "usage protocol," including identification of recommended dose levels, the time of day of administration, the time of administration within a work shift or during adjustments to shift changes, any limitations for the duration of treatment with modafinil (e.g., weeks or months), and determination of whether or not there are interactions with other chemical compounds that drivers frequently ingest, especially caffeine and antihistamines.

Caffeine

Caffeine (1,3,7-trimethylxanthine) and the related methylxanthines theobromine (3,7-dimethylxanthine) and theophylline (1,3-dimethylxanthine) are alkaloid compounds widely found in plants throughout the world. According to the Institute of Medicine (IOM) Committee on Military Nutrition Research (IOM-CMNR 2001), more than 60 different plant species contain caffeine. The primary sources of these compounds are coffee (*Caffea arabica*), kola nuts (*Cola acuminate*), tea

(*Thea sinensis*), and chocolate (*Coca bean*). In addition to appearing in omnipresent coffees, teas, chocolates, and other widely known sources caffeine is also available in alternative, convenient pharmaceutical packages of tablets or pills, from 50- to 300-mg doses (e.g., Vivarin® and NoDoz®), in the form of caffeinated chewing gum (e.g., StayAlert™ or Jolt Energy Gum™), is contained in some candies and breath mints (e.g., HyperMints™ or Euromints™), and is even available as caffeine-charged, bottled, noncarbonated natural spring clear water (e.g., Edge2-0™) and other caffeine-charged water products (e.g., Java Water, Aqua Java, Water Joe™, Potenza™, and FYXX Hybrid Water™). Some truck stops sell chocolate-covered roasted coffee beans to munch on to provide drivers with a "special picker-upper" while driving. Also readily available in many grocery stores and in most highway rest stop convenience stores are numerous beverages advertised as "energy drinks," commonly referred to as functional energy drinks (FEDs), wherein the major ingredient is caffeine, which is usually mixed with other caffeine-like chemicals (e.g., guarana) as well as other psychoactive ingredients. FEDs are described separately in chapter five under supplements.

Caffeine is the most widely consumed psychoactive or CNS stimulant in the world (Smith and Tola 1998). In addition to its natural occurrence in some foods and coffee, caffeine is used commercially as a food additive, and as a drug or a component of many pharmaceutical preparations. When administered in the amounts commonly found in foods, beverages, and drugs, caffeine has measurable effects on certain types of human performance. Caffeine use has been associated with increased alertness and enhanced physical performance, and as a countermeasure to the effects of sleep deprivation. Extensive research has been done on each of these effects of caffeine. Interested readers are encouraged to consult IOM's excellent summary of research findings on the efficacy of caffeine use (IOM-CMNR 2001), and the book *Caffeine* by Spiller (1998).

Caffeine is most often ingested by drinking some of the most popular and ubiquitous beverages such as coffee, tea, coca, colas, sodas, or other soft drinks that contain sizeable amounts of the stimulant. There is a wide range in the amount of caffeine in these beverages. The amount of caffeine in a cup of coffee is dependent on: (1) the source, quality, and quantity of coffee beans used to make the coffee; (2) the distributor's chemical processing techniques; (3) whether the coffee is in whole-bean form or as coffee grounds; and (4) the particular brewing techniques selected for its preparation. In the United States, brewed cups of regular coffee normally contain approximately 75 to 250 mg of caffeine per 8-ounce cup. Popular specialized coffees served in restaurants; for example, espresso, lattes, and iced coffees vary in portion size (e.g., 8, 12, or 16 ounces per cup) and therefore vary in the amount of caffeine they contain, but rarely exceed 250 to 300 mg per cup. However, some espressos contain more caffeine, ranging from 10 to 90 mg of caffeine per 1-ounce serving, and therefore have a greater "kick" per cup. Boutique shop 16-ounce coffees may contain as much as 550 mg of caffeine. Decaffeinated coffees generally have less than 10 to 20 mg of caffeine per 8-ounce cup.

Ice teas sold commercially have a range of from about 6 mg to 60 mg of caffeine in a typical 8-ounce serving. The FDA limits soft drinks to 71 mg of caffeine per 12 ounces. Depending on the particular brand, many commercial soft drinks (bottle or can) in the United States contain anywhere from 45 to 125 mg of caffeine per 12-ounce drink. Most but not all diet soft drinks are devoid of caffeine. For a comprehensive chart of the caffeine content of popular ingestibles, including soft drinks, caffeinated waters, chocolates, and medications, see Mitler and O'Malley (2005) and a popular Internet website listing amounts of caffeine in many beverages: http://www.energyfiend.com/the-caffeine-database.

Caffeine ingested in beverages (e.g., in coffee) enters the body through the digestive process, and is absorbed by the stomach within 30 to 60 min after oral administration. Caffeine is rapidly and completely absorbed in humans, with 99% being absorbed within 45 min of ingestion. The peak absorption time for caffeine received in pill or liquid form occurs before 60 to 90 min. Plasma concentrations may be influenced by the route and form of administration or other components of the diet, and the peak may range between 20 and 120 min after oral ingestion. Once absorbed, caffeine is distributed rapidly throughout body water. Caffeine is sufficiently lipophilic to pass through all biological membranes and it readily crosses the blood–brain barrier. The mean half-life of caffeine in plasma of healthy individuals is normally about 3 to 5 h, although its half-life may range between 1.5 and 9.5 h. This wide variation in reported half-life may be the result of individual variation in excretion rates or whether the individual smokes (which decreases half-life) or uses oral contraceptives (increases half-life). The pharmacological effects of caffeine (similar to those of other methylxanthines) include mild stimulation and wakefulness, the ability to sustain intellectual activity, and decreased reaction times (IOM-CMNR 2001).

U.S. Army medical researchers demonstrated that caffeine in chewing gum form (StayAlert™), which promotes caffeine absorption through saliva in the mouth, exhibits noticeable alerting effects in approximately 7 min. Peak absorption of caffeine from chewing gum occurs in 30 min (Kamimori et al. 2002; McLellan et al. 2003, 2005a, b). This application provides a much faster "picker-upper" when a person is particularly drowsy, but for practical reasons cannot cease work for a nap. Caffeinated chewing gum would appear to offer good application potential for commercial drivers.

The observable, subjective effects of caffeine last about 4 h and may include a sense or feeling of experiencing a slightly higher heart rate and elevated body temperature, a noticeable perky mood, increased alertness, and signs of improved cognition (i.e., reaction time and memory) and

physical performance. Caffeine consumed both at rest and during exercise increases a variety of physiological processes (heart rate, respiratory rate, blood pressure), most likely through the secretion of epinephrine, and includes cardiovascular, respiratory, renal, and smooth muscle effects. Caffeine has been touted as an ergogenic aid for enhancing physical performance, both aerobic and anaerobic functions, and muscular endurance as it increases arousal in the CNS, which may lead to reduced perception of the intensity of physical effort put forth (Cole et al. 1996; Baranski et al. 2001, TTCP 2001; IOM-CMNR 2001). Caffeine use is associated with a reproducible increase in endurance time in physical activities of moderate intensity and long duration. It has been shown to improve pulmonary function and aerobic performance, and it may also improve anaerobic performance while improving orthostatic tolerance as well. In describing caffeine's effects on voluntary muscle activation, the Hoffman reflex, motor-evoked potentials, self-sustained firing, pain, and sensation, Kalmar and Cafarelli (2004) suggested that caffeine may be useful in the study of central fatigue. Caffeine's effectiveness in enhancing either physical or cognitive performance dissipates within 24 h.

The effects of caffeine on cognitive performance are diverse. Behavioral measures indicate a general improvement in the efficiency of information processing after caffeine, whereas EEG data support the general belief that caffeine acts as a stimulant. Studies using event-related potential measures have indicated that caffeine has an effect on attention, independent of specific stimulus characteristics. Behavioral effects on response-related processes are mainly related to more peripheral motor processes.

Caffeine has been demonstrated to improve or enhance vigilance and alertness in both rested and sleep-deprived individuals. Caffeine is shown to improve and maintain psychomotor performance and a variety of cognitive functions during prolonged wakefulness (Hogervorst et al. 1999; Hindmarch 2000). Foskett et al. (2008) demonstrated that prior caffeine ingestion improved soccer players' passing accuracy and ball control. Military medical research labs demonstrated caffeine to be effective during situations involving combat-like stress (IOM-CMNR 2001; TTCP 2001). Its' effectiveness is related to the dose of caffeine ingested (Baranski et al. 2001). Owing to its low abuse potential and wide availability, caffeine offers significant utility for use in workplace fatigue countermeasures. For example, caffeine was used successfully to sustain aircrew alertness during flights over Iraq in support of Operation Southern Watch in August 1992 (Belland and Bissell 1994).

The IOM report on caffeine states that although both common experience and the results of scientific investigations support the belief that caffeine enhances performance on a variety of cognitive tasks, a review of the experimental literature reveals inconsistencies in the amount of caffeine required to produce positive effects on cognitive behavior. The discrepant findings are explained by differences among experiments in the number of variables, including whether or not subjects were tested following a period in which they had abstained from using caffeine just before the test, the tasks used to assess cognitive behavior, the age and gender of the participants, the subjects' longer term history of caffeine use, and whether the test subjects were rested or sleep-deprived. There has been some debate about whether caffeine enhances cognitive performance or simply restores degraded performance following caffeine withdrawal in rested individuals [James 1994, 1995, 1998; for further details consult the full IOM report (IOM-CMNR 2001)].

As is the case with most stimulants, the body adapts or adjusts somewhat to the intake of caffeine, and therefore some tolerance occurs with prolonged use of caffeine. Daily heavy coffee drinkers build up a degree of tolerance to the point that when they want to obtain an acute "jolt" from taking in caffeine, perhaps to temporarily restore alertness, that person needs to take in a higher dose of caffeine to feel the desired effects. This is why commercial drivers attending the FMCSA-ATRI lectures on "mastering alertness and managing driver fatigue" are told as a part of a strategy for fatigue management to use caffeine sparingly most of the time, and to conserve their timing for caffeine intake until they absolutely need a boost (e.g., in the middle of the circadian lull of the mid-afternoon). At that time it is recommended that drivers take in 1 to 2 cups of caffeinated coffee or beverages (O'Neill et al. 1996; Krueger and Brewster 2002, 2005).

Chronic high caffeine users, when they abruptly stop, may experience symptoms of withdrawal, including fatigue, depression, headache, nausea, and muscle spasms; the most likely withdrawal symptom is a "caffeine withdrawal headache" (Baranski et al. 2001; TTCP 2001). The best way to reduce withdrawal symptoms is to, over time, gradually lower the caffeine dosage (i.e., drink less caffeinated coffee). Drinking just another cup of caffeinated coffee usually helps dissipate a caffeine withdrawal headache.

Some research with caffeine suggests that it can enhance performance on some types of cognitive tasks and elevate some aspects of mood in rested individuals independent of its ability to reverse symptoms of withdrawal and regardless of the background consumption of caffeine. Warburton (1995) demonstrated that caffeine administered in doses of 0.75 mg and 150 mg to adult male, nonsmoking, regular caffeine users, without abstinence from caffeine before treatment, improved attention, problem solving, and delayed recall, and it significantly improved mood ratings. Rogers et al. (1995), using caffeine doses of 0 (placebo), 70, and 250 mg/day in caffeine users (>200 mg/day) and nonusers (<15 mg/day), demonstrated that although caffeine withdrawal had a negative effect on mood, it did not affect psychomotor performance. Jarvis (1993) reported the results of a large survey on coffee and tea consumption showing a highly significant dose-response relationship between habitual caffeine intake and psychomotor performance, simple reaction time, choice reaction time, incidental verbal memory, and visuospatial reasoning. This report demonstrated that tolerance to the performance-enhancing

effects of caffeine, if it occurs at all, is incomplete, with the result that higher daily caffeine consumers tend to perform better than do low consumers.

By employing a variety of standardized tests, caffeine's effects on cognitive function and mood can be detected in rested individuals, both users and nonusers of caffeine. Studies demonstrate that 200 mg (or more) of caffeine is efficacious in maintaining or returning cognitive performance to a rested level (Lieberman et al. 1987; Lieberman 2001). Only certain behavioral functions appear to be susceptible to the influence of moderate doses (32–256 mg) of caffeine. In particular, in well-rested individuals, low and moderate doses of caffeine preferentially affect functions related to vigilance (i.e., the ability to maintain alertness and appropriate responsiveness to the external environment for sustained periods of time), but have limited effects on memory and problem-solving abilities. Higher doses of caffeine (above 300 mg) can interfere with the performance of tasks requiring fine motor control (Durlach 1998; Rogers and Dernoncourt 1998) and may even produce other adverse effects, especially promoting high blood pressure (Kamimori 2000; Baranski et al. 2001).

With regard to commercial drivers' use of caffeine, a principal interest is its ability to assist in restoring alertness, especially when a person is at least partially sleep-deprived. Judicious use of caffeine can restore alertness, performance on mental tasks, and positive mood states. Smith and Rubin (1999) found that caffeine had a similar profile to amphetamines in that caffeine reversed sleep-deprivation-induced longer response times, and reduced the number of errors on a visual vigilance task, as well as the sleep deprivation-induced decrements in a running memory test. Bonnet and Arand (1994) found that caffeine increased alertness and performance on a visual vigilance task, mental arithmetic tests, and logical reasoning in sleep-deprived subjects. Caffeine has also been demonstrated to be effective in simulated combat-like conditions. The military found caffeine to be an effective cognitive aid in rested, sleep-deprived, and stressed warfighters (TTCP 2001). Research suggests that doses of caffeine between 150 and 600 mg are effective in alleviating sleep-deprivation-induced decrements in cognitive performance (Penetar et al. 1994; Kelly et al. 1996). Caffeine is also effective in delaying sleep onset in sleep-deprived subjects (Penetar et al. 1993, 1994; Smith 1999; Bonnet 1999).

In an attempt to determine if low-dose repeated administration of caffeine would be effective in work periods requiring extended wakefulness, Wyatt et al. (2004) determined that 0.3 mg of caffeine per kilogram of body weight, administered each hour for 29 h of wake episodes, is effective in countering the detrimental performance effects of sustained operations. In the war zones of Iraq and Afghanistan, U.S. military forces have routinely been issuing caffeinated chewing gum (100 mg of caffeine per stick of gum) for just such countermeasure applications to partial sleep loss (Kamimori et al. 2002; McLellan et al. 2003–2004, 2005). Such a strategy could be evaluated for its application to commercial driving scenarios.

Researchers at the Walter Reed Army Institute of Research compared and evaluated several stimulant compounds (including caffeine, modafinil, and dextroamphetamine) for their effects on complex cognitive processes subsumed under the construct of executive functions (Wesensten et al. 2005b; Killgore et al. 2009). Executive functions include a broad spectrum of complex higher-order cognitive abilities necessary to plan and coordinate actions, to monitor and adjust behavior, and to focus attention and suppress distractions. In a double-blind placebo-controlled study, Killgore et al. (2009) directly compared the effects of three stimulants (caffeine, modafinil, and dextroamphetamine) by examining specific aspects of executive function and working memory measured by the Tower of London (i.e., planning and visuospatial working memory), Tower of Hanoi (planning, strategy, sequencing, inhibition of pre-potent responses), and the Wisconsin Card Sorting Test (abstract concept formation, mental set shifting) in individuals deprived of sleep for two consecutive nights. After being awake for 45 to 50 h, participants were tested on computerized versions of the three tests. At the doses tested (caffeine 600 mg, modafinil 400 mg, or dextroamphetamine 20 mg) the modafinil and dextroamphetamine groups completed the Tower of London task in significantly fewer moves than the placebo group, and the modafinil group demonstrated greater deliberation before making moves. In contrast, subjects receiving caffeine completed the Tower of Hanoi task in fewer moves than all three of the other groups, although speed of completion was not influenced by the stimulants. Finally, the modafinil group outperformed all other groups on indices of perseverative responding and perseverative errors from the Wisconsin Card Sorting Test. Killgore et al. (2009) concluded that each stimulant may produce differential advantages depending on the cognitive demands of the task.

Caffeine and Driving Performance

Although many studies examined either the effects of fatigue on driving or of caffeine on cognitive or psychomotor performance, little attention has been paid to the interaction of caffeine and fatigue on driving-related skills (Gibson et al. 2006). Studies reporting the effects of caffeine on actual driving performance usually involved automobile simulators (e.g., Heatherly et al. 2004). Several studies focused on comparisons of caffeine to nap taking or other sleep-related variables. For example, Biggs and colleagues (2007) studied driver's perceptions of simulated driving performance after sleep restriction and caffeine. Whereas caffeine improved measures of lane drift, the relationship between perceived and actual performance after fatigue countermeasures remained inconclusive. In a French study, two dozen drivers took an on-the-road driving test between 2:00 a.m. and 3:30 a.m. after being given either a placebo (decaffeinated coffee), regular coffee, or were allowed to take a 30-min nap. Highway lane crossings were counted as the measure of interest because lane crossings are involved in many sleep-related crashes. During the 90-min drives, the decaf drinkers recorded a total of 159 lane crossings while drowsy (during the early morning

drives), compared with just 2 lane crossings during daytime pretest data collection drives. Those who took naps did better than the drivers who drank decaf, crossing lines only 84 times. However, the coffee drinkers (with caffeine) did the best in the early morning drives, crossing lines a total of 27 times (Philip et al. 2006; Sagaspe et al. 2007).

In quest of suitable countermeasures to drowsy driving, other researchers sought to combine techniques of napping and ingesting caffeine. Such is the case with car simulator research done by Horne and Reyner (1996), whose studies confirm that consuming caffeinated coffee just before taking a short nap (~20 min) and then resuming driving may be an effective strategy to sustain acceptable driving performance—a strategy that has been advocated for commercial drivers as well, particularly in the afternoon circadian lull (G. Krueger's fatigue and alertness courses for FMCSA and ATRI, held more than 100 times from 1996 to 2006).

Subsequent research by DeValck and Cluydts (2001) and DeValck et al. (2003) determined that both a 300-mg dose of slow-release caffeine and a 30-min nap were successful in counteracting a driver's sleepiness in a partial sleep deprivation study. The remedial effect of slow-release caffeine lasted longer than that of the nap and was also effective in afternoon sessions. They declared slow-release caffeine to be a valuable countermeasure, and suggested that it is preferable to even a short nap.

Laboratory studies of similar issues, but without including a driving component, appear to verify the utility of the combined countermeasure techniques. Schweitzer et al. (2006) evaluated the effects of combining naps with administration of caffeine on performance and alertness in both laboratory and field settings. In the lab study (a parallel groups design), 68 healthy participants were assigned to 1 of 4 experimental conditions: (1) participants in one group were given an evening nap opportunity before the first 2 of 4 consecutive, simulated night shifts plus placebo taken all 4 nights; or (2) caffeine (4 mg/kg) taken nightly; (3) others got the combination of the nap and caffeine condition; and (4) the fourth group received a placebo. The *laboratory study* found that napping, caffeine, and their combination all improved alertness and performance as measured by Maintenance of Wakefulness Tests and by the Psychomotor Vigilance Task (PVT); however, the combination of napping and caffeine was best in improving alertness. In their *field study*, 53 shiftworkers who worked nights or rotating shifts were permitted an evening nap on the first 2 of 4 consecutive night shifts plus taking caffeine nightly, versus shiftworkers who took a placebo nightly without being allowed to take naps. Napping plus caffeine improved performance as measured by the Psychomotor Vigilance Task (faster reaction times) and decreased subjective sleepiness in individuals working the night shift. Schweitzer et al. (2006) concluded that napping plus caffeine helps improve performance and alertness of night-shift workers.

Parliament et al. (2000) provided a comprehensive review of recent developments in the flavor and chemistry of caffeinated beverages, predominately updating research on coffee, tea, and cocoa. Their collection of 40 papers is based on a March 1999 symposium on the topic to specifically address antioxidative phenolic compounds found in the beverages, and to examine health benefits, such as the anticancer, anti-aging, and heart disease prevention properties of these beverages. Select papers in this volume also describe health benefits of "green tea" (Chen and Fong 2000; Hara 2000) and present an analysis of coffee phenols and phenolic acids (Cohen 2000).

Assessment of caffeine. In summary, caffeine is a relatively safe and effective means of maintaining or restoring cognitive performance even under conditions of operational stress (e.g., Baranski et al. 2001; IOM-CMNR 2001; Caldwell et al. 2009). Caffeine restores cognitive function during prolonged wakefulness and it can enhance certain types of cognitive performance, most notably vigilance and reaction times in rested individuals regardless of whether or not they are regular caffeine users. The doses of caffeine most likely to be effective without causing undesirable mood effects are within the range of 100 to 600 mg.

The amounts of caffeine cited for regular soft drinks, or for single cups of coffee, may appear somewhat low compared with the doses administered in some of the laboratory experiments cited in this synthesis. However, it is often the number of caffeinated drinks consumed by a person in short duration that determines the amount of caffeine consumed and the resultant effect on the CNS, including impact on alertness, cognitive enhancement, degree of blood pressure changes, nervousness experienced, and other known effects. Heavy caffeine consumers, including many commercial drivers (G. P. Krueger, personal communications, 1996–2006), often drink 10 or more cups of caffeinated coffee or 10 or more caffeinated soft drinks (even FEDs) per day.

The paucity of actual highway driving studies examining effects of caffeine suggests that more research on this obvious fatigue countermeasure needs to be conducted to delineate numerous unanswered usage protocol variables for commercial driver alertness management and fatigue countermeasure programs. Questions should be addressed that identify for commercial drivers when to use caffeine, in what doses, what format (e.g., beverages, tablets, chewing gum, and timed release capsules), how often, and what effects should be anticipated; for example, clarifying how long before preparing to sleep should one refrain from its use, etc. In particular, additional research should be done on the potential for use of slow-time-released caffeine capsules and on caffeinated chewing gum applications. The studies by Horne and Reyner (1996), those of DeValck and Cluydts (2001), and De Valck et al. (2003), and the work of Schweitzer et al. (2006) suggest that additional research on caffeine, particularly slow-release caffeine, in conjunction with judicious nap taking, may lead to valuable fatigue countermeasure applications for long-haul commercial drivers.

Cautions of caffeine use. As with any stimulant there are risks in consuming too much caffeine too regularly

(IOM-CMNR 2001). Certainly, it is inadvisable to regularly drink too much caffeinated coffee and continually subject the body to a slightly elevated blood pressure. Drinking coffee in moderation is always recommended. Some studies, with caffeine doses ranging from 100 to 600 mg per day, found that caffeine use occasionally may result in mild gastrointestinal problems, insomnia, anxiety, restlessness, diuresis leading to dehydration, and increased physiological tremor. With higher doses of caffeine, intakes of 1 g of caffeine (15 mg/kg), mild side effects have been observed progressing from restlessness, nervousness, and irritability to more serious effects such as delirium, nausea, emesis, and neuromuscular tremors. At extreme high doses (e.g., 10 g) caffeine can cause vomiting, convulsions, and even death. The fatal acute oral dose of caffeine in humans is estimated to be between 10 and 14 g (150 and 200 mg/kg) (IOM-CMNR 2001).

Nicotine

Nicotine is classified as a stimulant. It is also classified as a relaxant, primarily because it increases levels of dopamine in the brain (a hormone/neurotransmitter that causes sensations of pleasure). Nicotine increases heart rate, blood pressure, and respiratory function. It produces pleasure by attaching to the nicotinic acetylcholine receptor on certain nerve cells, which in response release the chemical signal glutamate, telling connected neurons to release dopamine. The more the nerve cells are excited, the more dopamine is released and the more pleasant the feeling (McGehee et al. 2002).

Nicotine is readily available in the form of several tobacco sources, including ubiquitous cigarettes, cigars, and chewing tobacco. It is also available in the form of nicotine skin patches (subcutaneous), nicotine chewing gum (polacrilex), and other products predominately advertised for assistance in smoking cessation plans.

Research interest in the effects of nicotine and tobacco smoking on human performance has waxed and waned since the early 1900s (Heishman 1998). In the 1990s, owing to renewed attention from the scientific and public health policy communities, a significant amount of research was conducted in programs such as those sponsored by NIDA. Extensive literature reviews by Sherwood (1993) and by Heishman et al. (1994) generally concurred that nicotine enhances a limited range of behavior and has complex effects on human performance, but that any performance improvements are small in magnitude. The appearance of these review articles prompted numerous additional studies that examined the effects of nicotine and smoking on performance, especially cognitive functioning (Heishman 1998).

Much like the considerations involving caffeine studies, interpretation of the performance effects of nicotine depends in part on whether it was tested under conditions of nicotine-deprivation or nondeprivation. That is, effects are dependent on whether a research subject is in a state of tobacco deprivation (i.e., nicotine withdrawal) or whether he or she is a nonsmoker and therefore a newcomer to tobacco/nicotine use (Heishman et al. 1994; Ernst et al. 2001). In nicotine-dependent individuals, tobacco deprivation (withdrawal) can impair attentional and cognitive abilities within 12 h of smoking cessation (Gross et al. 1993; Lyvers et al. 1994; Bell et al. 1999). Reinitiating nicotine administration or cigarette smoking can reverse such performance deficits to pre-deprivation levels (Parrott and Roberts 1991; Bell and Jacobs 1999). Today, the topic of nicotine deprivation and performance is very much prevalent in transportation industries because, for example, some airlines enforce no-smoking policies for their pilots, potentially bringing about flight performance decrements in pilots who are smokers (see flight simulator research on this subject by Mumenthaler et al. 1998, 2003, 2010).

Whether improved performance associated with relief from withdrawal should be considered cognitive enhancement, or simply labeled *restoral* to baseline performance levels, has been questioned (Hughes 1991; Heishman et al. 1994). Heishman (1998) pointed out that few studies examined the cognitive effects of a history of smoking, and research reports do not often report pre-deprivation performance levels of test participants. The absence of such data makes it difficult to determine whether nicotine functions to reverse deprivation-induced performance decrements or if it produces true behavioral enhancement. Although nicotine appears to have been shown to, at least in part, reverse deprivation-induced deficits in performance, conversely true enhancement of performance has yet to be clearly demonstrated either in nonsmokers or nondeprived smokers (Heishman 1998). True enhancement would be most effectively demonstrated if nicotine or smoking were shown to facilitate or improve performance in nonsmokers or in nonabstinent smokers (Heishman et al. 1994; Heishman 1998; Ernst et al. 2001).

Relatively few placebo-controlled studies have examined the acute effects of nicotine taken in through smoking (Sherwood 1993; Heishman et al. 1994; Heishman 1998; Ernst et al. 2001). The findings of numerous nicotine studies have been inconsistent (Perkins et al. 1990, 1994; Foulds et al. 1996; Ernst et al. 2001). The results in many studies have been discrepant, including improved performance in motor responses (LeHouezec et al. 1994; Bates et al. 1995), sustained attention, and recognition memory, but no effect or impairment in selective attention (Foulds et al. 1996), conditioned learning, and recall memory (Ernst et al. 2001). No studies report true enhancement of sensory abilities, or improvements in cognitive abilities such as problem solving and reasoning (Heishman 1998). Foulds et al. (1996) reported that subcutaneous nicotine (skin patches) improved response time on a logical reasoning test in nicotine-deprived smokers, but had no effect in nonsmokers. Most study reports do not critique whether laboratory measures generalize to performance in the real world.

Ernst et al. (2001) examined the influence of past smoking history on cognitive performance by comparing 4 mg of acute

nicotine administration (polacrilex gum) and placebo in 12-h abstinent smokers to that of ex-smokers and nonsmokers. An improvement effect of acute nicotine administration (independent of smoking history) was seen only with respect to reaction time on a 2-letter search task. Working memory performance was related to smoking history (smokers performed most poorly and never smokers were best). A logical reasoning task showed no effects of either acute or chronic nicotine exposure. Ernst et al. concluded that nicotine may influence the focusing of attention in smokers as well as nonsmokers, and that trait-like differences in some cognitive domains, such as working memory, may be either long-term effects or etiological factors related to smoking.

The literature includes several studies of nicotine and simulator driving performance. Other studies reported nicotine effects on laboratory tests meant to be representative of driving-like tasks. The studies depict a wide variation in designs, and produce conflicting and somewhat inconclusive results. As one example, Sherwood (1995) examined the psychomotor effects of acute administration of single smoked cigarettes with varying amounts of nicotine (<0.1, 0.6, 1.0, or 2.1 mg) on a 1-h computer-based driving simulation (four times in 4 days) comprising continuous tracking and brake reaction time tasks. Brake reaction times were decreased as they improved over all active treatment levels of nicotine; however, tracking accuracy was enhanced after only two cigarettes of middle strength were smoked. Sherwood concluded that cigarette smoking may improve driving performance, and that there may be an optimal nicotine dose for the enhancement of cognitive and psychomotor functions. However, making conclusive statements about the effects of smoking based on such short-duration studies (employing only 1 h drives) can be misleading.

In a flight simulator study, Mumenthaler et al. (1998, 2003) showed that nicotine improved scores on individual flight tasks such as approach to landing, a task that requires sustained attention; they concluded that nicotine may improve late-day flight performance in nonsmoking aviators. Mumenthaler et al. (2010) also demonstrated that nicotine withdrawal effects for smoker-pilots, who are not allowed to smoke in the flight deck, exhibit adverse affects on their simulator flight performance.

Perhaps the most pertinent psychological performance study examining nicotine applications for alertness enhancement during continuous operations (but also d-amphetamine) is that of Newhouse et al. (1989, 1992). In that Walter Reed study, nicotine was infused intravenously at doses of 0.25, 0.37, and 0.5 mg after 48 h of wakefulness. They found that nicotine had no significant impact on MSLT measures or on psychomotor performance. Additionally, nicotine did not effectively improve cognitive performance (as measured on several tests in the Walter Reed cognitive Performance Assessment Battery); nor did nicotine improve alertness. This prompted Newhouse et al. (1992) to conclude that nicotine was "not an effective stimulant for maintaining cognitive alertness during sustained performance operations." Therefore, contrary to widespread and common belief, the study by Newhouse et al. demonstrated that nicotine may not be an effective stimulant for maintaining alertness during sustained performance operations.

The ambient smoke associated with burning cigarettes in the cab or operator compartment of one's vehicle is likely to add to driver drowsiness. This is in part because exposure to tobacco smoke adds to carboxyhemoglobin in the blood, and it cuts down on oxygen flow within the bloodstream (Benignus 1991). In addition, cigarette and cigar smoke tend to be irritants to the eyes and nasal passages. Some commercial drivers insist that during lengthy drives they stop to take a walk-around smoke break to help restore alertness. In so doing, the rest break away from driving, especially the act of walking around produces some recuperative alertness value in the form of overall bodily stimulation. Given Heishman's (1998) assessments of nicotine's "restoral of alertness" to smoker withdrawal, and the results of research such as that of Newhouse et al. (1992), it is reasonable to conclude the recuperation in alertness during the drivers' smoke breaks is not likely attributable to the nicotine consumed per se, as much as it is probably the result of the "restoral effect" for nicotine deprived smokers, and to the physical stimulation effected by the exercise gained by walking around in the fresh air outside the truck.

Research sponsorship. Turner and Spilich (2006) reviewed a sample of 91 published papers investigating the effects of tobacco or nicotine use on cognitive performance. This review is cited here because Turner and Spilich's principal aim was to determine if the pattern of conclusions drawn by researchers acknowledging tobacco industry financial support differed from the pattern of conclusions drawn by researchers who apparently did not have tobacco industry support. Scientists acknowledging tobacco industry support typically reported that nicotine or smoking improved cognitive performance, whereas researchers not reporting financial support from the tobacco industry were more nearly split on their conclusions. The authors concluded that the existence of a possible bias in the published literature according to a funding source must be given serious consideration (Turner and Spilich 2006). The same cautions should pertain to pharmaceutical industry-sponsored studies of any chemical substance or new drug.

Assessment of nicotine. The health risks of tobacco use and smoking have been well-publicized for more than a quarter of a century and by now should be well-known by everyone. Risks of cancer, heart and lung disease, hypertension, and cardiovascular and circulatory problems prevail as health risks from smoking and tobacco use. For all of these health-risk-related reasons, this synthesis does not support recommendations for use of nicotine-containing tobacco (cigarettes, cigars, or chewing tobacco) for maintaining alertness during commercial driving. Nor does it support nicotine administration by means of skin patches or gum form with commercial drivers, although more research on these aspects of the nicotine topic may be warranted.

Nicotine Treatment for Smoking Cessation

Nicotine polacrilex gum, when used properly, has been demonstrated to be an effective medication for treatment of nicotine dependence (*U.S. Surgeon General's Report* 1988). Nicotine polacrilex can provide therapeutic effects such as the reduction of tobacco withdrawal symptoms, reduction of the tendency to smoke cigarettes, reduction of the effect of relapse factors such as weight gain, and possibly reduction of urges to smoke (Henningfield et al. 1990). However, all of these actions of nicotine are related to the dose level actually being obtained, and inadequate nicotine doses may produce no beneficial effect (Henningfield and Woodson 1989). Often, it appears that patients use nicotine polacrilex with insufficient instruction either to obtain adequate dose levels or to achieve specific benefits (Cummings et al. 1988; Jarvik and Henningfield 1988). For many patients who were unable to quit smoking with the use of nicotine polacrilex, the problem may have been a failure to obtain the medication in sufficient doses and not medication failure per se (Henningfield et al. 1990).

Insomnia and daytime fatigue and sleepiness are recognized as one of the criteria for nicotine withdrawal syndrome (Underner et al. 2006). Nicotine replacement therapy could be potentially hazardous to individuals whose occupations require alertness, such as drivers of commercial vehicles, because of the effect of the nicotine replacement disrupting sleep and causing unusual and distressing dreams (Colrain et al. 2004).

When nicotine is placed in the mouth, the amount actually absorbed through the buccal mucosa is determined by the pH of the salvia, because nicotine is a weak organic base that is best absorbed in the nonionic form. Nicotine absorption can be substantially impaired by consumption of acidic drinks such as coffee and carbonated beverages (fruit juices and soft drinks) either while using the polacrilex (chewing gum) or immediately before using polacrilex. For details, see a review, and published research on this topic by Henningfield et al. (1990).

Smoking Cessation Drug Warning

At a time when many commercial drivers are attempting to stop smoking or to cease using chewing tobacco, it is important to note that use of a popular smoking-cessation prescription drug, varenicline (Chantix™), warranted dangerous side effects warnings, as issued by three U.S. federal agencies, the FDA, FAA, and FMCSA (May 2008). The drug acts at sites in the brain affected by nicotine and may help those who wish to stop smoking by providing some "nicotine-like" effects to ease the withdrawal symptoms and by blocking the effects of nicotine from cigarettes if users resume smoking. An Institute for Safe Medication Practices review of hundreds of "adverse event" reports (2007) forwarded to the FDA by Chantix maker Pfizer Pharmaceutical identified immediate safety concerns about the use of varenicline among persons operating aircraft, trains, buses, and other vehicles or in other settings where a lapse in alertness or motor control could lead to massive, serious injury. The Institute reported that more than 1,000 complications linked to varenicline were reported in the first quarter of 2008, including 15 traffic accidents, 52 incidents of loss of consciousness and blackouts, and 50 deaths.

On May 16, 2008, the FDA became convinced that varenicline (Chantix™) had serious side effects and exhibited symptoms including anxiety, nervousness, tension, depressed mood, unusual behaviors, and thinking about or attempting suicide. The FAA removed Chantix™ from the list of medications considered safe for pilots and air traffic controllers. On May 23, 2008, the FMCSA issued an advisory warning stating that varenicline (Chantix™) may adversely affect commercial drivers' ability to operate vehicles safely, and that medical examiners should not certify a driver taking Chantix™.

Another medication used for smoking cessation, bupropion (Wellbutrin® or Zyban®) is also associated with adverse effects, including insomnia, tremors, agitation, rash, and confusion. Kolber et al. (2003) and Ross and Williams (2005) reported that with concomitant use of tramadol (Ultram®) the threshold for seizure is lower, and interactions of the two medications promotes additional side effects.

Erectile Dysfunction (anti-impotence) Medications

Erectile dysfunction (ED) medications do not fit neatly into the category of stimulant drugs; however, for the sake of including them in this synthesis, their description is presented here. Several medications used for treatment of ED are some of the most popular and widely used drugs in the United States and Europe (e.g., sildenafil and vardenafil) (Kloner and Zusman 1999). Contrary to popular belief, sildenafil is not an aphrodiasiac, does not work in the absence of sexual arousal, and does not make a potent man more virile (DeMey 1998). After oral administration, sildenafil is rapidly absorbed, reaching peak plasma concentrations in 30 to 120 min. For pharmacokinetic details on sildenafil see Johnson and Lewis (2006).

Vardenafil (Levitra®) was introduced in the United States in 2003, but currently is not one of the most widely prescribed treatments for ED, as other newer ED medications are more popular. After oral administration of vardenafil, peak plasma concentrations are obtained within 30 to 60 min. Vardenafil and its active metabolite have a terminal half-life of approximately 4 to 5 h (Johnson et al. 2006).

Johnson et al. (2006) pointed out that although they are relatively safe, the several ED medications available have certain side effects that present a possibility of creating safety

hazards in aviation operations. One such potential side effect is a condition known as "blue tinge"—the inability to discriminate between blue and green colors, which could hinder execution of certain tasks such as a pilot relying on instruments during adverse meteorological conditions and/or during night flights (Borrillo 1998). Additionally, vardenafil has been shown to potentiate the hypotensive effects of nitrates commonly employed in treatment of certain heart conditions (Bischoff 2004). Work at FAA's CAMI is directed at chemical postmortem analysis of biological samples taken from pilots who died in airplane crashes. Those numbers demonstrate increases in postmortem ED medications found in pilots. What effect or role the ED medications have played in recent aircraft crashes has not yet been determined (Johnson et al. 2006; Johnson and Lewis 2006). Monitoring those investigations is warranted to determine if there are safety-related parallels in the commercial driving industry.

No reports evaluating the cognitive performance effects of taking ED or anti-impotence medications were located. However, unconfirmed news accounts report that several military forces have been doing exploratory research on sildenafil (Viagra®) to assess its efficacy in assisting high-altitude fighter pilots to fight off fatigue and "foggy heads." The hypothesis is that the ED family of drugs might be effective in these conditions because when there is a long shortage of oxygen, such as during flight at high altitude, it leads to pulmonary hypertension ("high blood pressure in the lungs") and the drugs could help fight that condition by improving the flow of oxygen through the body. This may be counteracted by supplemental oxygen available or required for pilots flying above certain altitudes. Israeli Air Force research began after some exploratory work in other low oxygen environments, such as those concerning mountain climbers on extremely high mountain climbs (*Times of London*, Feb. 7, 2008). The active ingredient in Cialis® (tadalafil) helped climbers ward off fatigue and dizziness at greater altitudes (Richalet et al. 2005).

ED medication assessment. Although neither potential benefits nor significant problem areas were identified with the use of ED medications during driving operations, it is incumbent on the commercial driving community to continue to monitor research results and other medical developments, particularly any revealing adverse events attributable to use of these popular medications.

Table 3 summarizes in tabular form some of the basic information concerning stimulants and wake-promoting chemical substances and their possible uses.

TABLE 3
LIST OF STIMULANTS AND WAKE PROMOTING SUBSTANCES

Category	Availability	Use/Effect	Comments
Permitted for CMV drivers			
Caffeine	Ubiquitous, in coffee, tea, soft drinks, energy drinks, tablets, and so on	Alertness maintenance, slight boost to energy	Need for operations usage protocol and guidance; highlight risks; e.g., high BP
Nicotine	Tobacco use, smoking, skin patches	Soothing with smoking habit	Not effective for restoring or maintaining alertness performance; causes cancer
Functional Energy Drinks (FEDs) [see see chapter five: nutritional supplements]	Energy drinks, chews, candies, supplements	Popular drinks with hopes for slight stimulant effects	No substantive research data on effects; risk of taking too many FEDS, interactions with other chemicals possible
Modafinil	Only with prescription; mostly as prescription for ProVigil® for SWSD or ADHD	Rx for SWSD, ADHD, Narcolepsy Stimulant without untoward effects	Promising for alertness, but not yet commonly accepted for CMV driver use Need more research and usage protocol guidance
Generally Not Permissible for CMV Drivers			
Amphetamines:	Legally available by prescription for medical treatment only, 391.41.b-12	Stimulation helps sustain performance, but with other undesirable effects	Risk of loss of CDL or job if caught using without prescription
d-amphetamine	Controlled operational applications limited to military		Used for short-duration military applications; use not likely permissible in CMV operations
Methamphetamine Methylphenidate	Prescription and on the street	Treatment for ADHD	Not practical, risk of abuse
Cocaine	Illicit; bought on the streets	Recreational, addictive	Risk of loss of CDL, job
Ephederine	FDA cautions; still available	Mostly a weight loss fat burner	Can be dangerous

BP = blood pressure; SWSD = shiftwork sleep disorder; ADHD = Attention Deficit Hyperactivity Disorder.

CHAPTER FIVE

SUPPLEMENTS: NUTRITIONAL, HERBAL, ENERGY BOOSTERS, DIETARY, AND HEALTH FOODS

INTRODUCTION TO SUPPLEMENTS

Every year the dietary and nutritional supplement industries introduce another proliferation of chemical compounds in enticing new formats (i.e., energy-boost drinks, bottled flavored water augmented with vitamin mixes, nutritional supplement candy chews, caffeine-infused chewing gum, high-energy food bars, lose-weight crash-diet measures, and so on). Marketers engage popular professional athletes and other celebrities in splashy advertising designed to encourage consumers to use such products to achieve a better, more healthful or exciting lifestyle. However, manufacturers offer little published medical and human performance research data to support or back up advertising claims about many such supplements.

This chapter covers a variety of chemical substances and/or psychoactive compounds that commercial drivers might ingest on occasion, but which do not fit neatly into the two categories of hypnotics and stimulants described in chapters three and four. This encompassing chapter includes coverage of traditional nutritional, herbal, and health food supplements; relaxants; insomnia treatments; dietary compounds used to control a person's weight; and energy boosters such as drinks, candies, and gums. Many of these products are augmented with active chemical ingredients, some of which are psychoactive. Certainly these have effects on performance; the principal concern here being their effects on vehicle operator performance. These consumer products are available across the counter in grocery, convenience, and drug stores; in health food shops; and at shopping center kiosks. Importantly, many of them are readily available in convenience shops not far from the fuel pumps at highway rest stops. This chapter attempts to outline what is known about these chemical substances, and to identify the supplements that appear to warrant additional research to determine their efficacy and their safety issues relating to truck and bus/motorcoach drivers.

DEFINITIONS OF SUPPLEMENTS

A dietary supplement is normally thought of as a product taken by mouth that contains an "ingredient" intended to beneficially supplement what one normally eats. The Dietary Supplement Health and Education Act (DSHEA) of 1994 places dietary supplements in a special category under the general umbrella of "foods," not drugs, and requires that every such ingredient or combination of ingredients be labeled as dietary supplements. Manufacturers of supplements are responsible for ensuring the safety of the ingredient(s), but by statute the FDA is not authorized to require data supporting safety from the manufacturer, as it does for food additives or drugs (see the FDA website on Center for Food Safety and Nutrition at: http://www.cfsan.fda.gov and Kurtzweil 1999; GAO-09-250 2009).

Dietary supplements are widely available through a rapidly expanding market of products commonly advertised as beneficial for better health, performance enhancement, and disease prevention (IOM report: Greenwood and Oria 2008). The "dietary ingredients" in these products may include vitamins, minerals, herbs, other botanicals, amino acids, and substances such as enzymes, organ tissues, and gland tissue or secretions. Dietary supplements can be extracts or concentrates, and may be found in many forms including tablets, capsules, gel caps, liquids, and powders, and in food bars, flavored candy-like chews, and chewing gum. Information on their label must not represent the product as a medication, as a conventional food, or as a sole item of a meal or diet. An ergogenic aid is defined as anything that helps enhance energy utilization and usually promotes physical performance in the body. Nutritional supplements such as sports drinks (e.g., Gatorade™) or those meant for inclusion in meals might be classified as ergogenic aids. An ergolytic agent is anything that possesses the ability to decrease work output such as exhibiting a negative effect on muscle activity (U.S. Army CHPPM 2004).

Dietary supplements available to commercial drivers range from those that might impart beneficial effects, to better health and performance with negligible side effects, to others that have uncertain benefits and that potentially might be harmful to health and performance. The challenge is to determine which supplements fall into each of these two categories. In the United States there are no commercial transportation-wide policies regarding dietary supplements. Some safety concerns over supplements, especially the lack of appropriate guidance for their use, were described when IOM assessed supplements for the military (Greenwood and Oria 2008). The paucity of medical guidance for use of supplements prompts similar concerns that commercial drivers who take supplements might inadvertently compromise their own performance or health. Without usable information and guidance, drivers also might forgo taking dietary supplements that potentially could improve their performance or health.

Nutritionists portray how what we eat or consume can help us achieve adequate or even optimal performance levels

(McArdle et al. 1991). Dr. C. Everett Koop, former Surgeon General of the U.S. Public Health Service, was fond of saying "we are what we eat" as he cautioned Americans that most of the ten frequent disease killers in our society are related to what we eat. Nutrition experts recommend a balanced diet high in complex carbohydrates and low in fat to help individuals attain peak performance. Although it is true that some supplements may provide health benefits, others are unnecessary, because in a proper diet the food we eat should be able to supply all the nutrients, vitamins, and minerals our bodies require. Additionally, many supplements, if taken incorrectly, or if they happen to contain metals, toxicants, or much larger doses of whatever identifiable compound the consumer thought he or she was taking, can cause risks to one's health. Ubiquitous advertisements promote many pills, powders, gels, drinks, and more to help a person gain weight or muscle mass, to lose weight, or to simply feel better; or they promise to make one faster or stronger, and so on.

An evaluation of the numerous dietary supplements available is especially difficult because many such products contain multiple ingredients, they can have a changing composition over time, or because individuals use them intermittently at doses that tend to be difficult to measure, and mostly the amounts ingested are not recorded (IOM report: Greenwood and Oria 2008). The descriptions that follow do not lend themselves to orderly "clumping" of supplement products into categories. The attempt here is to describe chemical substances that are widely included in commercial products; in particular, highlighting those that contain psychoactive ingredients that in some way might affect the performance or health of commercial drivers who take them.

In an attempt to be somewhat comprehensive, this synthesis also provides modest coverage of other ingestible items that do not strictly qualify as nutritional supplements per se (e.g., drinking appropriate amounts of water to sustain proper hydration); however, they are included in this report because such practices involve additional chemical substances (e.g., fluoride and/or sodium and minerals contained in drinking water) that may impact driver health or performance. Again, the emphasis in the main body of this chapter is predominately to describe substances with psychoactive effects. In cases where the synthesis team did not identify sufficiently strong evidence in the scientific literature, we relegated what we have to say about those substances (supplements or not) to Appendix C to this report. Such is the case, for example, with several of the herbal substances used as relaxants; stress and tension alleviants, for sleep-inducing supplements involving amino acids; and with the use of daily multi-vitamins. In the cases where the scientific evidence identified for psychoactive effects was slim, those descriptions appear in the Appendix C of this report (see Table 4).

Caveat, a general caution: Most nutritional, health, and dietary supplements sold commercially (e.g., in health food shops or grocery stores) are not approved by the FDA. Many of these chemical components are covered under the Federal Dietary Supplement Act. However, because the quality of dietary supplements is not regulated by the FDA, their production is not regulated by the Good Manufacturing Practices Act. The contents and quality of dietary and nutritional supplements on the store shelves varies dramatically. There is no guarantee that the labeling of the contents in packaging accurately depicts what the package, bottle, or other container actually holds. Objective validation of claims of safety or efficacy is not readily available. The supplement business is a "buyers beware" marketplace (Kurtzweil 1999; Straus 2002; GAO 2009).

Consumers therefore must exercise caution with all health food supplements. Products imported to the United States from overseas suppliers, especially some products in the pharmaceutical and food industries, have perpetually raised issues of manufacturing quality assurance. Depending on the source or supplier, the manufacturing standards for these compounds is not always in accordance with the quality assurance that might be found for products typically monitored for compliance in the U.S. market. There have been instances in which herbal and health supplements or component ingredients acquired from overseas, especially those purchased over the Internet, were contaminated with toxic metals or with other drugs. Federal government agency (e.g., FDA, NIDA, and DEA) alerts and warnings about hazardous products sometimes lag months behind outbreaks of problems with such imported purchases. To minimize the risks of contamination health food, dietary, and herbal supplements should be purchased only from reliable sources. Determining what constitutes a reliable source can at times be problematic.

PSYCHOACTIVE HERBAL SUPPLEMENTS

Guarana (Paullinia cupana)

Guarana comes from the seeds of a South American plant—a shrub—the vast majority of which is grown in a small area in northern Brazil. Guarana gum or paste is derived from the seeds, rich in xanthenes approximately equivalent to caffeine. Guarana paste is inserted into herbal supplements to food and beverages. Viewed as a tonic in South America, and especially so in Brazil, for decades guarana has been inserted into numerous soft drinks much the way caffeine is added to soft drinks in the United States. Now, guarana is increasingly found in drink products in the United States. In Japan, guarana extract formerly was incorporated into chewing gum, and advertised to prevent drowsiness (Sato et al. 1984).

Because the major active guarana constituent "guaranine" is nearly identical to caffeine, guarana is claimed to be an effective energy booster and is likely to have similar physiological and behavioral effects to those of caffeine. Guarana also contains similar related alkaloids such as theobromine and theophylline—both of which are also found in coffee and tea (Bertrand and Carneiro 1932; Bempong and Houghton 1992; Bempong et al. 1993; Leung and Foster 1996; Walker et al. 2000; TTCP 2001). Each of these compounds has well-

TABLE 4
LIST OF SUPPLEMENTS AFFECTING HEALTH AND PERFORMANCE

Category	Where Found	Use/Effect	Comments
Herbals			
Guarana Ginkgo Biloba	Health food stores, truck stops, inserted into soft drinks and energy drinks	Mild stimulants; have some effect on cognitive and reaction time performance	Some studies indicate mild effects akin to those of caffeine. No adverse effects demonstrated
Ginseng, Passion Flower, Kava Kava, Valerian, St. Johns Wort	Health food stores, boutique over-the-counter shops	Relaxants to alleviate tension, stress, induce sleep	Psychoactive effects not substantiated, relegated write-up to report's appendix
Physical Performance Enhancers			
Carbohydrates	White rice, bread, pasta, and sugars	Can improve/maintain physical performance	As restorative can improve memory
Amino Acids: Tryptophan, Tyrosine	Health food stores, found in meats	Tyrosine helpful for stress resistance; some sleep improvements	Scant evidence of cognitive performance enhancements
Multi-vitamins, Minerals and Antioxidants	Purchased in numerous stores	Replace/supplement bodily needs not met through good nutrition	Not likely to improve performance; but may speed energy recovery
Anabolic Steroids	Naturally in body, available through athletic outlets	DHEA for muscle building and popular with longevists	Can enhance well-being, but also impair cognition; must continue treatment to prevent loss of effects
Hydration			
Water	Ubiquitous supply; now available in bottles everywhere	Essential nutrient; proven benefits to the body	Bottled water may contain sodium and minerals, not fluoride
Vitamin and Mineral Drinks/Waters	Sold in grocery stores	Feel good drinking them vs. sodas	Not much noticeable effect, taste is okay
Functional Energy Drinks (FEDs)	In many stores and highway rest stops	Belief they restore or boost energy; used as alcohol drink mix	FEDs contain large amounts of caffeine, taurine, sugar, etc.
Energy Bars, Chews, etc.	Stores, truck stops	Energy boost, picker-uppers, suppress hunger	Not enough data to verify energy boost effects
Dietary and Weight Loss Products	Health food stores, diet clubs, over the Internet	To lose weight; mostly in fad dieting	Often contain multiple substances not verified for efficacy or safety

known effects as nervous system stimulants. As such they also have some effect on increasing metabolic rate, suppressing appetite, and enhancing both physical and mental performance, and they have a mild diuretic effect. Guarana has been said to decrease fatigue, reduce hunger, help with arthritis, and has been used to treat diarrhea. Guarana has a history of use in treating hangovers from alcohol abuse and headaches related to menstruation (Duke 1985).

The mode of action with guarana is primarily attributable to methylxanthine alkaloid caffeine. Guarana's effects on the CNS therefore are similar to those of caffeine. The duration of effects is similar to that of free caffeine at about 3 to 5 h. Guarana contains about twice the caffeine found in coffee beans (about 3% to 4% caffeine in guarana seeds as compared with 1% to 2% for coffee beans). Concentrated guarana extract powders contain caffeine at levels of as much as 40% to 50%. Thus, 5 g of guarana at 3.5% to 5.6% caffeine, taken less than 1 h before activity, will make approximately 175 to 280 mg of caffeine available in the body at the time of commencement of the activity (TTCP 2001). Popular South American guarana supplements deliver about 50 to 200 mg of caffeine per day (similar to the amount found in 1 to 2 cups of strong coffee).

Guarana extract powder, providing 500 to 1,000 mg of guaranine, is claimed to provide mild stimulant properties and enhanced physical and mental performance. Higher levels of intake have not been demonstrated to provide additional increases in performance, but may result in adverse side effects such as tension, irritability, and nausea. Guarana mostly acts as a cognitive enhancer through increased catecholamine production. The likely psychoactive effectiveness of caffeine probably also applies to guarana. Claimed benefits are that guarana improves mood and cognitive performance, and assists in fighting fatigue.

In one of the earliest published studies on guarana's effects on performance, Galduroz and Carlini (1994, 1996) conducted a long-term study on normal, elderly, adult subjects, but found no significant psychoactive effects on thinking or mental functions. However, in lab studies with healthy young adults, Kennedy et al. (2004) demonstrated the psychoactive effects and the cognition-enhancing properties of guarana. These researchers gave 75 mg of a dried ethanolic extract of guarana (approximately 12% caffeine), 200 mg of Panax ginseng, and a combination of the two (75 mg/200 mg) to 28 healthy young participants (ages 18 to 24) in a multi-day study. Cognitive performance and subjective mood were assessed pre-dose

and at 1, 2.5, 4, and 6 h post-dose using serial subtraction tasks and mood scales from the cognitive drug research (CDR) computerized assessment battery. Throughout the day, all three treatments resulted in improved task performance compared with placebo. For guarana, improvements were seen across attention tasks (but with reduced accuracy) and on a sentence verification task. Both ginseng and the ginseng/guarana combination increased the speed of attention task performance, and enhanced speed of memory task performance, but exhibited little evidence of modulated accuracy. Guarana, and the combination of guarana with ginseng, and to a lesser extent ginseng itself, led to significant improvements in serial subtraction task performance.

In another study, Kennedy et al. (2008) assessed the acute effects of either a mix of vitamin/mineral/guarana supplement or placebo drink in 129 healthy young adults (ages 18 to 24). Thirty minutes post-dose, participants completed six consecutive runs on a 10-min battery of cognitive demand tests (i.e., 60 min of testing). The vitamin/mineral/guarana combination resulted in improved task performance in comparison with placebo in terms of increased speed and accuracy of performing a rapid visual information processing task. While on the supplement mix, subjects reported attenuation of mental fatigue on a mental fatigue scale.

Few other experimental studies of guarana were located. The findings of Kennedy et al. apparently have not yet been replicated. Therefore, one cannot yet strongly support statements regarding the cognitive performance benefits of guarana.

As with caffeine, guarana also is likely to be effective in enhancing physical performance when a person is working at a high percentage of aerobic capacity. Guarana may have moderate positive effects on anaerobic performance and muscular endurance.

Guarana tends to suppress appetite and therefore is potentially useful for weight loss and obesity control. Neither guarana, nor simply caffeine by itself, appear to be especially effective as stand-alone weight loss aids; however, in combination with other thermogenic and nervous system stimulants, guaranine or caffeine may extend the activity and potency of certain supplement ingredients. As with any caffeine-containing substance, too much guarana can lead to nervousness, tension, and headaches. No long-term adverse consequences have been reported with guarana (TTCP 2001).

In the United States, the commercial bottled drink industry and marketers of energy boost compounds recently began inserting considerable amounts of guarana into their products, along with other psychoactive compounds (including caffeine, taurine, and ginseng). Guarana is found in some soft drinks, colas, lemonade, energy drinks, supplement powders, and food bars. Many of these new products containing guarana are found on the "energy boost product shelves" at truck stops along major highways in the United States.

Assessment of guarana. The work of Kennedy et al. (2004, 2008) indicates the potential of guarana use for bringing about positive effects on cognitive performance. Because guarana has already invaded the supplement marketplace in the United States, further research on guarana appears warranted. Studies are needed to examine the effects of typical doses of guarana individually as well as synergistically when combined with other psychoactive ingredients currently in food supplements available on the store shelves. Further, educational materials about the make-up of guarana and its potential effects on health and performance are needed for the user public, and for commercial drivers and for their employers.

Ginkgo Biloba

For thousands of years extracts and infusions made from the leaves of the small bushy Ginkgo Biloba tree have been used in traditional Chinese medicine for treatment of a variety of problems including asthma and digestive disorders. Ginkgo biloba represents one of the most studied and commonly used herbal remedies in the world. In many western countries, especially in Europe, the use of an extract made from the green ginkgo leaf serves as a popular OTC herbal supplement advertised for its antioxidant properties, and as a prescribed remedy for use on a number of vascular problems, treatment of memory loss, dementia, and macular degeneration (O'Hara et al. 1998). Ginkgo biloba's popularity grew in the United States during the late 1990s and it continues through today. In 2002, the National Health Interview Survey found that ginkgo was the third most popular natural product in the United States and determined that ginkgo was being used in some form by about 4% of American adults.

Two main groups of active constituents responsible for ginkgo biloba's medicinal effects are terpene lactones and ginkgo flavone glycosides, present in varying concentrations in the leaf of the ginkgo tree. Ginkgo effects may arise from a single active ingredient or by the combined actions of the many active ingredients. Approximately 40 different flavonoids have been isolated. Commercial extracts of ginkgo are generally standardized with regard to the content of the primary active components, with the flavone glycosides and terpenoids compromising 24% and 6% of the total extract, respectively. At the physiological level, ginkgo extract is both a platelet-activating factor antagonist and a free radical scavenger. The exact mode of action of ginkgo biloba in the body is not precisely known. The bioactive properties of ginkgo biloba extracts are varied. Ginkgo appears to modulate a number of neurotransmitter systems and it exerts effects on cellular metabolism. These and other mechanisms underlie a number of reported health effects of ginkgo, including improvements in blood circulation and neuroprotective roles after various neuronal insults (Kennedy et al. 2000), for treatment of certain forms of tinnitus (ringing in the ears), for short-term memory loss, for senile dementia, and as a blood thinner to prevent stroke. As therapy, the usual dosage has been 120 to 240 mg

of ginkgo biloba daily, or 40 to 120 mg as a prophylactic brain tonic (Kleijnen and Knipschild 1992).

There is a lack of standardization of ginkgo biloba extracts in the supplement marketplace, making dose comparisons across studies difficult. Little information has been published regarding the pharmacokinetics, pharmacodynamics, and/or the duration of ginkgo effects (Gilbert 1997). Preliminary data for some active ingredients give a time-to-peak plasma at 1 to 3 h and a half-life of 3 to 6 h. A usual dose of ginkgo extract ranges from 120 to 600 mg. Chronic treatments usually administer 120 mg of ginkgo daily for up to 6 weeks, and this has demonstrated no adverse effect on performance of healthy young subjects.

Ginkgo is said to improve aspects of cognitive performance. Claims for ginkgo extract include those suggesting it enhances mental function in healthy individuals and that it has been shown to be effective in the elderly for "cerebral insufficiency" (an imprecise term describing memory loss, confusion, depression, dizziness, and tinnitus). More than 400 animal and clinical trials looking at a variety of medicinal properties and clinical uses for ginkgo biloba suggested that its purported cognitive-enhancing effects are most likely attributable to its flavonoid and ginkgolide compounds (the latter found nowhere else in nature), which may arise from uptake inhibition and enhanced release of neurotransmitters (Kleijnen and Knipschild 1992).

Kennedy et al. (2000) examined ginkgo extract (at doses of 120 mg, 240 mg, and 360 mg) for cognitive performance effects, at 1, 2.5, 4, and 6 h after administration using measures from the CDR computerized assessment battery. Ginkgo produced a number of significant changes on performance measures, the most striking of which was a dose-dependent improvement of the "speed of attention" factor following both the 240- and 360-mg doses, which was evident at 2.5 h, and was still present at 6 h after administration. Additionally, there were time- and dose-specific changes in performance (positive and negative) on the other three cognitive factors (accuracy of attention, speed of memory, and quality of memory) of the CDR. Across three such experiments, the effects of the 120-mg dose of ginkgo (normal dose level) on cognitive speed were equivocal, even appearing to have a negative effect on speed of attention task performance; only modest effects were demonstrated in memory task performance (Kennedy et al. 2000, 2007; Scholey and Kennedy 2002). There were improvements in self-rated mood following ginkgo, and to a lesser extent a combination product (ginkgo, guarana, and vitamin mix) as well (Kennedy et al. 2002).

Some studies reported that ginkgo improved memory in healthy subjects, but an absence of effects on other cognitive tasks (Warot et al. 1991; Wesnes et al. 1997; Rigney et al. 1999). Rigney et al. (1999) reported positive ginkgo extract effects (acutely administered) were more pronounced for memory, particularly working memory, and the effects demonstrated were dose-dependent, but not in a linear dose-related manner. They concluded that the cognitive-enhancing effects of ginkgo are more likely to be apparent in individuals aged 50 to 59 years. Elsewhere, beneficial effects of ginkgo on cognitive performance have been reported after 4 to 6 weeks of treatment in elderly individuals and for those suffering from dementia.

Using a similar test paradigm to the one previously mentioned, Kennedy et al. (2001) examined the combined effect of administering both ginkgo biloba and Panax ginseng on cognitive performance, memory, and mood. They gave a combination dose of 320, 640, and 960 mg, along with a matching placebo, to 20 healthy young adult volunteers, and tested at 1, 2.5, 4, and 6 h after the day's treatment. The most striking result was a dose-dependent improvement in performance on a "quality of memory" factor for the higher dose. This effect appeared targeted at secondary memory rather than the working memory component. There was also a dose-dependent decrement in performance of the "speed of attention" factor for both the 320- and 640-mg doses.

Canter and Ernst (2007) reviewed 15 studies with randomized, placebo-controlled, double-blind clinical trials looking for the effects of standardized ginkgo biloba extracts on cognitive function. They did not find enough convincing evidence for a robust positive effect of ginkgo biloba on any aspect of cognitive function in healthy young individuals after either acute or longer-term administration. Thus, of the few studies with healthy young subjects, the only effects of ginkgo have been modest improvements in memory. No reports described cognitive performance of healthy individuals being impaired by ginkgo extract.

Assessment of ginkgo biloba. Canter and Ernst (2007) presented what may appear to be a convincing indictment. In reality, there were not a sufficient number of reportable studies of ginkgo biloba and cognitive or psychomotor performance to make definitive statements in this synthesis about the efficaciousness or utility of ginkgo biloba to meet the primary interests of the commercial driving community. Additional targeted research might help elucidate these issues.

Herbal and Nutritional Supplement Remedies to Relieve Stress and Tension, and Promote Relaxation and Sleep

Proponents of nutritional supplements advocate various herbs to relieve stress. These herbal compounds include Passion Flower, Lavender Oil, Kava, Valerian, Ginseng, and Saint John's Wort. Additional nutrient supplements that help with anxiety or stress are proteins such as 5-HTP, and amino acids such as Tryptophan, Tyrosine, and Theanine. Most of these supplement products are commercially available in boutique health food stores, nutrition shops, and in some grocery stores. Although the synthesis team identified some descriptive and scientific reports of studies of their effects on health and

performance, for many of these substances the evidence of their importance as psychoactive substances that might impact commercial driver performance was not significant. These are described in Appendix C.

ENERGY SUPPLEMENT DRINKS, FOOD BARS, CANDY CHEWS, AND OTHERS

Caffeine was described extensively as a stimulant in chapter four. It was pointed out that caffeine shows up in numerous products best described as supplement drinks, and in supplement food bars and gels, advertised to boost one's energy level. This section describes caffeine (in its various forms), along with other psychoactive substances included as ingredients in many of the "energy supplements" readily available in most highway rest stop convenience stores, grocery stores, and so on.

Functional Energy Drinks

Since the late 1990s, energy drinks (sometimes called caffeinated FEDs) have become popular, especially so with young adults, producing a growing health concern for adolescents (Babu et al. 2008). The major ingredient in the numerous energy drinks is caffeine, mixed along with other caffeine-like chemicals (e.g., guarana), as well as several other psychoactive ingredients. The range of caffeine in popular FEDs may be from 80 mg to as high as 500 mg of caffeine per serving—which means the caffeine in a single energy drink (of some brands) can exceed that of two six-packs of Cocoa Cola (Reissig et al. 2009).

Individuals who consume FEDs give many reasons for why they partake of energy drinks, including because they (1) give a burst of energy, (2) help the consumer to stay awake, (3) increase alertness, (4) improve short-term memory, (5) help students perform better on tests, and (6) mixing alcohol with an energy drink can reduce the severity of a hangover, protect the liver, and keep a person from getting drowsy. College students commonly mix energy drinks with alcohol, leading to numerous complications (Malinauskas et al. 2007; O'Brien et al. 2008). Whereas electrolyte replacement sports drinks (e.g., Gatorade®) attempt to replenish the body after strenuous activity or exercise, FEDs do not replenish the body. Mixing a FED and alcohol can significantly dehydrate a person because both substances have diuretic effects (Reisenhuber et al. 2006). In a lab study, Ferreria et al. (2006) demonstrated that the subjective perceptions of headache, weakness, dry mouth, and impairment of motor coordination were less intense when alcohol was combined with an energy drink. However, objective measures of motor coordination, visual reaction time, and breath alcohol concentration for energy drink plus alcohol were the same as for alcohol alone. Ferreria et al.'s results basically showed that a person subjectively feels less intoxicated than they actually may be. This point was accentuated by the FDA when in the fall of 2010 it pressured the company Physion Projects into withdrawing its alcoholic energy drink "Four Loko™" beer from the marketplace after numerous adverse life-threatening events implicating consumption of quantities of the combination alcohol–caffeine drink occurred on college campuses in the United States.

To remain within the spirit of the 1994 Dietary Supplement Health and Education Act, manufacturers of energy drinks claim the ingredients in FEDs are derived from healthy substances, such as vitamins, herbs, and other natural ingredients. Because the FDA does not regulate such supplements, the manufacturer bears the full responsibility for ensuring the product is both effective and safe for human consumption and use. The ingredients must be listed in the "other ingredients" section instead of the "supplement facts" section on product labeling; however, the specific amounts do not have to be included, and typically manufacturers do not list them.

Grosz and Szatmari (2008) indicate there is a paucity of published detail on either the contents or descriptions of the human effects of FEDs. Red Bull™ is the most widely known energy drink, as it is sold in more than 140 countries. Most of the popularly marketed FEDs such as Red Bull™ are made up predominately of sugar water and contain fruit juice flavoring and high levels of caffeine and taurine and other herbal stimulants as the principal "active ingredients," along with small amounts of glucuronolactone, niacin (niacinamide), sodium citrate, and inositol. Other FED ingredients may include guarana, ginseng, and orange rind extract. The manufacturers of these drinks claim their stimulating effects are the result of interaction among the various ingredients and they claim the drinks improve physical endurance, reaction speed, and concentration. Among the many commercially available FEDs, one competing brand called "Yellow Jacket Energy Drink" for example is advertised to provide "Twice the Buzz, helping to deliver energy one needs to get through the day."

In addition to caffeine as a major ingredient, some of the more common ingredients also found in many FEDs include:

- Taurine—known as 2-aminoethane-sulfonic acid. In 1827, taurine was originally isolated from bull or ox bile (taurus means bull in Latin), but now is available synthetically for insertion into energy products. It is produced in the liver and in the brain where it serves as an inhibitory neurotransmitter exerting neuroprotective effects against excitotoxic agents and oxidative stress such as those released during an ischemic episode (Chepkova et al. 2002; Kim 2003). Taurine is the most abundant free amino acid in many body tissues. Taurine is different from other amino acids in that it is not incorporated into proteins. It plays an important role in osmolarity regulation and in metabolism and it is found in

high concentrations in skeletal muscles where it plays an important role in modulating contractile function. In some cases taurine acts as a mild sedative and as an age-defying antioxidant. It also has potential to steady irregular heartbeats. Only a small number of studies have been published to validate many of the beneficial claims attributed to taurine, especially its claimed beneficial effects in energy drinks.

- Glucuronolactone—a natural compound found in the body, about which little is documented. Users of energy drinks generally believe glucuronolactone fights fatigue and increases well-being; however, little has been published about its inclusion in FEDs (600 mg in a 250 ml can of Red Bull™), thus its effects are not clear (Clauson et al. 2003).
- Niacin—also known as vitamin B-3, among other functions, it helps increase so-called good cholesterol (HDL) by preventing the formation of triglycerides, making it a useful cholesterol control drug. There usually is not enough niacin in FEDs to provide this benefit. The niacin contained in the energy drinks (20 mg in a 250 ml can of Red Bull) is not pure enough to give the mild head rush dubbed the "niacin flush" (Clauson et al. 2003). Not much has been reported about potential interactive effects of niacin, if any, with other compounds found in FEDs.
- Inositol—a carbohydrate found in animal muscle it is sometimes called "meat sugar." Inositol is a water-soluble fatty lipid, a part of the vitamin B complex (B8) required for formation of healthy cells. It promotes healthy brain development and function, and works closely with choline to move fats out of the heart and liver. Inositol is used for treatment of diabetic nerve pain, panic disorder, high cholesterol, insomnia, cancer, depression, schizophrenia, Alzheimer's disease, ADHD, autism, promoting hair growth, and the skin disorder psoriasis. There usually is so little inositol in energy drinks (50 mg in a can of Red Bull), that its potential benefits on the body are deemed to be negligible. As a paradox for the drink manufacturers, consumption of large amounts of caffeine may cause a shortage of inositol in the body; thus, heavy coffee drinkers may benefit slightly from taking supplemental inositol.

The manufacturers of energy drinks such as Red Bull™ tout the likely combination of energizing effects by placing caffeine along with other ingredients such as taurine (1,000 mg) and glucuronolactone (600 mg) into the beverage (Mayer 2002). Several researchers (Woojae 2003; Van den Eynde et al. 2008) attempted to "debunk" the likely impact of taurine in favor of indicating that it is predominately the caffeine that brings about the energetic effects (desirable or undesirable). Woojae (2003) reported this is likely to be true regarding the increase in cardiac stroke volume witnessed by Baum and Weiss (2001); it pertains as well to the shorter reaction times and improved effects on emotional well-being reported by Seidel et al. (2000), the increased alertness reported by Alford et al. (2001), and improved information processing times reported by Warburton et al. (2001)—all of which were more likely affected by the amounts of caffeine administered than they were by the taurine (Woojae 2003). Woojae argues that the endogenous taurine found in high concentrations in skeletal muscles self-regulates itself and the taurine levels are maintained at a stable level in the brain as well. One can of Red Bull™ is reported to contain between 65 and 80 mg of caffeine, about the same amount of caffeine as can be found in many normal brewed cups of coffee. Thus, Woojae suggests that it is not likely that supplemental taurine would have much effect; it is more likely that the higher caffeine levels in the drinks are responsible for the effects observed when drinking Red Bull or other similar energy drinks, particularly so when quantities of the drink are consumed (Woojae 2003).

In examining several popular FEDs, Clauson et al. (2003) determined that most of them contain products such as guarana, ginseng, and taurine in such small amounts that they are far below the amounts expected to deliver either therapeutic benefits or adverse events. By comparison, the drinks usually contain as much as 80 to 300 mg of caffeine and 35 g of processed sugar per 8-ounce serving, amounts known to cause a variety of adverse health effects. Commonly reported adverse effects seen with the amounts of caffeine present in the energy drinks are insomnia, nervousness, headache, and tachycardia.

Both caffeine and taurine have direct effects on cardiac function and hemodynamic status. Steinke et al. (2007) assessed whether or not commonly consumed energy drinks alter the blood pressure, heart rate, and electrocardiogram (EKG) parameters in healthy participants. Participants consumed 500 mL (two cans) of an energy drink containing caffeine (80 mg) and taurine (1,000 mg). Blood pressure, heart rate, and EKG measures were repeated 30 min, 1, 2, and 4 h after consumption, over a 5-day test. Although no significant EKG changes were observed, subjects' heart rate increased 5 to 7 beats per minute (bpm), and systolic blood pressure increased 10 mm Hg after consuming an energy drink. They suggested these physiological levels are likely clinically significant for consumers who happen to have cardiac disease or for those individuals who regularly consume quantities of such energy drinks.

The study by Steinke et al. (2007) was performed on healthy subjects, and it cited amounts of taurine to be 1,000 mg (presumably akin to Red Bull at the time). Some energy drinks available in the year 2010 have increased the amounts of some of the potentially offending ingredients. Effects of such combinations of substances as these apparently have not been assessed on subjects with hypertension while they happen to be using various anti-hypertensive medications. Many commercial drivers suffer from hypertension and are being medicated for it, which should raise some concern. In August 2010, these synthesis authors purchased the popular product Monster

Hitman Energy Shooter™ from the OTC energy boost shelf at a local drug store and noted that the listed ingredients for the 3-ounce dietary supplement included 6 g of sugar; 45 mg of sodium; more than 200% of the recommended daily allowance for vitamins B-2, B-3, B-6, and B-12; 2,000 mg of taurine; 400 mg of ginseng; and a 5,000-mg energy blend of glucose, L-carnatine, caffeine, inositol, guarana, glucuronolactone, and maltodextrin. The label warns individuals not to consume more than one shot of Monster Hitman every 4 h.

Kennedy and Scholey (2004) demonstrated that some of the same cognitive performance effects are obtained through combinations of only caffeine and glucose, without adding the other substances into the energy drinks. Van den Eynde et al. (2008) tended to agree, stating that most of the effects of energy drinks on cognitive performance are related primarily to the presence of caffeine. They suggest further investigation is needed into the effects of the lesser known ingredients of energy drinks (e.g., taurine and glucuronolactone) to gain a better understanding of the possible interactions of the multiple substances.

Warburton et al. (2001) identified experimental design inadequacies in the literature (e.g., pre-test cutbacks on caffeine by participants that might have produced caffeine withdrawal during testing). Subsequently, they designed an experiment to examine whether or not test participants with minimal pre-test deprivation from caffeine would produce similar results to participants who ordinarily were asked to abstain from caffeine before their participation in experiments. They concluded that moderate doses of caffeine and taurine can improve information processing in individuals who could not have been in caffeine withdrawal at the time of their participation in the testing. Their caffeinated/taurine group of participants improved attention and verbal reasoning, but there was no significant effect on memory (Warburton et al. 2001).

Reyner and Horne (2002) investigated the effectiveness of a well-known FED for reducing sleepiness in drivers. After restricting their sleep to 5 h the night before, 12 healthy young adults drove a car simulator between 1400 and 1700 h. Following a pretreatment 30-min drive, participants were given 250 ml of a FED (containing sucrose, glucose, 80 mg caffeine, taurine, glucuronolactone, and vitamins: equivalent to Red Bull) versus a control drink with the same volume and taste but without the caffeine, taurine, and glucuronolactone. Two hours of continuous driving ensued. Compared with the controls, energy drink participants significantly reduced sleep-related (fatigue) driving incidents (e.g., lane drifts) and reported less subjective sleepiness for the first 90 min of the drive. There was a trend for the EEG to reflect less sleepiness during this period. It was concluded that FEDs can be beneficial in reducing sleepiness and sleep-related driving incidents during monotonous afternoon driving following modest sleep restriction the night before (Horne and Reyner 2001; Reyner and Horne 2002). Additional studies of this type should be pursued with commercial drivers in instrumented driving simulators as well.

Jay et al. (2006) did a crossover design experiment with 15 young adults, simulating a first night-shift protocol with two conditions: participants taking an energy drink (FED) and a baseline control (non-FED) condition. Both test conditions involved a period of extended wakefulness from 0700 on one day to 0730 hours the next (24.5 h awake), followed by an 8-h daytime recovery sleep (0730 to 1530 h). During the FED condition, an energy drink was administered twice during the night. Sleepiness was assessed during the period of extended wakefulness and for a further 6 h after awaking. Comparison of sleep periods (measured with EEG) showed that sleep onset latency remained unchanged, as did stage 2 and slow wave sleep. However, sleep efficiency was significantly reduced, and total sleep time was 29.1 min shorter in the FED condition. The study demonstrated the residual effects of the FED's active ingredients impacting on some aspects of daytime sleep following a simulated night shift. Subsequent performance however was unaffected. Jay et al. stated that the results deem FEDs effective for use in alertness control during a single night shift and warrant investigation into FED use over successive night shifts (Jay et al. 2006). Such calls for additional research should also be made for the commercial driving community, where the obvious applications and implications of FEDs should be pursued.

A major reason popular energy drinks raise public health concerns is because they contain high levels of caffeine, and typically not all the ingredients and the quantities of each are accurately labeled on popular products. In their review of a large variety of energy drinks, Reissig et al. (2009) stated that in the year 2006, annual worldwide energy drink consumption increased 17% from the previous year to 906 million gallons, with Thailand leading the world in energy drink consumption per person. The United States led the world in total volume sales. These Johns Hopkins researchers published tabular information about the caffeine contents in energy drinks by brand name, indicating that the caffeine content ranged from 50 mg to 505 mg per 12-ounce serving. One drink, a 1-ounce "ammo" drink, had the greatest concentration at 171 mg of caffeine per ounce of drink; whereas Red Bull™ was listed as having 9.6 mg of caffeine per ounce, or 67 mg caffeine per 8-ounce can. A commercially available product, SoBe's "No Fear" drink, contains 141 mg of caffeine per 16 ounces. Coca-Cola Classic had the least caffeine at 2.9 mg/oz.

With a concern that consumers may be unaware of the consequences of caffeine intoxication, Reissig et al. (2009) wrote that from 2002 to 2004 a U.S. poison control center received 42 cases of caffeine abuse from caffeine-enhanced beverages. Caffeine intoxication includes symptoms such as nervousness, anxiety, restlessness, insomnia, gastrointestinal upset, tremors, tachycardia, and psychomotor agitation. Clauson et al. (2003) found four case reports of caffeine-

associated deaths as well as four separate cases of seizures associated with the consumption of energy drinks. Reissig et al.'s review (2009) calls on the FDA to insist on requiring the manufacturers to disclose the amount of caffeine in energy drinks on the label of the containers.

Australian medical researchers tested 30 young adults 1 h before and 1 h after consuming one 20 ml can of sugar-free Red Bull (DeSciscio et al. 2008). In August 2008, these researchers publicly stated that just one can of the popular stimulant energy drink, Red Bull (whose marketing advertises "Red Bull gives you wings"), can increase the risk of heart attack or stroke, even in young persons (Reuters news articles, Canberra, Australia, Nov. 2008). The senior researcher, Scott Willoughby, reported that 1 h after volunteers drank Red Bull their blood systems were no longer normal, but were abnormal in a way that would be expected in a patient with cardiovascular disease. In an interview, Willoughby suggested the drink caused the blood to become "sticky," which he declared to be a pre-cursor to cardiovascular problems. Willoughby (2008) advises that Red Bull could cause important complications if combined with stress or high blood pressure, impairing proper blood vessel functioning and probably increasing the risk of blood clotting and stroke.

There have not been sufficient conclusive studies on the combined effects of caffeine and taurine in Red Bull™, Monster Hitman Energy Shooters™, or other FEDs, and the true contents and the full extent of health risks mostly are not listed on containers of such products. For these reasons, the popular drink Red Bull is banned in Norway, Uruguay, and Denmark. Nevertheless, it is still widely sold, and it was estimated that 3.5 billion cans of Red Bull have been sold in 143 countries around the world.

Assessment of functional energy drinks. Most of the FEDs available in the public marketplace advertise ingredients that include sugar, caffeine, taurine, and some vitamins or small amounts of other chemical substances, a few of them adding to the combination of psychoactive substances. The relatively small number of reputable studies in the literature mainly indicated that most of the psychoactive effects from the FEDs can be attributed to the concentration of caffeine contained. Effects owing to secondary substances, apparently added largely to satisfy marketing ploys, are likely to be slight. However, health and performance concerns remain about verifying the potential synergistic or interactive effects of the several ingredients found in FEDs, which individuals may consume in considerable quantity while they happen simultaneously to be taking medications and other chemical substances.

Several experiments described previously demonstrated the potential applicability of FEDs for reducing sleepiness and sleep-related driving incidents after sleep restriction (e.g., Reyner and Horne 2002). The effectiveness of FEDs was also shown during simulated first-night shift work, as highlighted by Jay et al. (2006); however, FEDs also adversely impacted recovery sleep on the following day.

Additional research with FEDs is called for, preferably to be conducted in driving simulators to elucidate the implications of judicious use of FEDs by commercial drivers. Subsequently, guidance about the measured effects of FEDs on health and performance would be appreciated in the commercial transportation industries.

Five- and Six-Hour Power Energy Booster Drinks

The earlier write-up on FEDs portrays a number of health concerns, particularly in consuming multiple servings or simultaneously mixing the popular FEDs in combination with alcohol. In part, in response to those reports, the energy drink industry now markets newer alternative energy drinks. Intense advertising on U.S. television and a wide availability in convenience stores, including truck fuel stops, has made two of these new drinks the best known to date: (1) the new "2-ounce shot": 5-Hour Energy™ drink (distributed by Living Essentials), and (2) another 2-ounce shot drink called 6-Hour Power™. Both products identify themselves as "vitamin supplement drinks."

The label on the 5-Hour Energy™ bottle, and the company's website, suggest that its unique blend of vitamins provides a boost of energy, and its combination of amino acids provides cognitive enhancements, such as an increased ability to focus and a better mood. The company's advertising says 5-Hour Energy™ is different from other energy drinks because it excludes guarana, contains only as much caffeine as is found in one cup of coffee, and it has "zero sugar, zero net carbohydrates, and only four calories." The lack of sugar and reduced amount of caffeine are said to eliminate the "crash effect," a reduction in energy below baseline that most users of other energy drinks (FEDs) experience owing to their high levels of sugar and high caffeine content. Living Essentials claims these drinks will make a person feel "awake, alert, and productive for hours—without the jitters and crash associated with other energy drinks"—and therefore 5-h energy is perfect for "combating a groggy morning, that afternoon lull, or to motivate you to work out."

The label on the bottle of the 5-Hour Energy™ drink indicates that it contains 30 mg of niacin, 40 mg of vitamin B-6, 400 mcg of folic acid, 500 mcg of vitamin 12 (as cyanocobalamin), and 0 mg of sodium. The energy blend of 1,870 mg of liquid contains taurine, glucuronolactone, malic acid, n-acetyl, l-tyrosine, l-phenylalanine, caffeine, and citicoline. Although the amount of caffeine contained is not specified, the instructions on the bottle warn consumers to limit themselves to "two *shots* of 5-Hour Energy a day, spaced hours apart." Thus, if the contents really only have the equivalent caffeine found in a cup of coffee, there would appear to be less of a risk of someone who properly uses 5-Hour Energy™ encountering difficulties attributable to consuming too much caffeine than

there would be in consuming the more widely known FEDs, each of which present significantly more caffeine. No confirmatory scientific data were located on this topic.

The company website for the 6-Hour Power vitamin supplement drink conveys minimal helpful information about their product. The ingredients listed on the bottle include vitamins B-6, B-12, and C; niacin; folic acid; sodium; an energy blend of taurine; malic acid; caffeine; tyrosine; and a blend of three enzymes.

Assessment of hour power booster drinks. Although these vitamin-laced drinks may not harm a person if taken according to the directions, there is also no published evidence that they have the efficacy and functional validity for safe on-the-road usage. For this synthesis, no research reports were located documenting the efficacy, safety, or cognitive effects and other performance and health implications of using either the 5-Hour Energy or the 6-Hour Power "shots."

Additional research is recommended on this potential alternative to the FEDs if for no other reason than they are apparently now being consumed by so many commercial drivers. Both products can be readily purchased in most drugstores and grocery stores, and at any truck stop along the nation's highways. It is not known how many of the super vitamin-laced drinks described here are being consumed by commercial drivers; however, anecdotal evidence from checkout clerks at three major truck stops along Interstate Route 95 noted that truck drivers appear to buy a lot of them, and "swear by them" (G. Krueger, personal communications, Aug. 2009).

ENERGY BOOST POWDERS, PILLS, FOOD BARS, ETC.

In a way similar to the energy drink market, there also are available a large number of "nutritional-energy boost" food bars, pills, tablets, powders, and so on, each being promoted as energy booster products containing herbs, vitamins, and minerals. Most of these present splashy colors and advertising displays, and offer to increase or enhance performance (whether it be physical or cognitive performance), alleviate stress, provide more energy, provide power to achieve, and so on.

The MaineWay synthesis team acquired a sampling of a dozen or more such energy boost items directly from truck rest stop stores along highways such as Interstate 95 from Florida to New York, and along Interstate 81 from Virginia through Pennsylvania (Figure 2). [Note that this photograph is for information purposes and is not intended as an endorsement of any kind.] These products touted, as energy

FIGURE 2 A sample of psychoactive supplements found at interstate highway convenience stores.

boosters, were in forms as varied as pills, powders, food bars, packets of capsules, gels, energy gums, mints, candies, chews, and more. Examining this sampling for their listed ingredients indicated that most claim to have combinations and mixes of such ingredients as ginseng; guarana; vitamins A, B, C, and E; niacin; folic acid; amino acids; beta carotene; bee pollen; various mineral mixes; bioflavonoids; and so on. These products are advertised as stress control and power booster formulas, and boast energy-max and energy-hit pickups. Most such products were prominently displayed on grocery shelves where truck drivers would be sure to see them as they frequent the establishments to refuel, visit the rest rooms, and/or to replenish convenience food supplies.

Assessment of vitamin energy boost products. No scientific reports examining or evaluating the three items mentioned previously (i.e., vitamin-laced drinks, electrolyte replacement drinks, or energy boost supplements in pill or bar forms) were located for documentation in this synthesis. Some laboratory research on these many products may be warranted. Controlled laboratory studies could be carried out to examine and report on the efficacy and safety of use of such readily available products by commercial drivers.

CHAPTER SIX

MEDICATIONS AND COMMERCIAL DRIVER MEDICAL CERTIFICATION: REPORT ON A SURVEY OF MEDICAL EXAMINERS OF COMMERCIAL DRIVERS

INTRODUCTION

Both prescribed medications and self-administered "over-the-counter" drugs may affect driver alertness, the onset of driver fatigue, and overall driver performance. Concerns have been raised about the association between drugs and medications as contributing factors to the cause of highway crashes.

The significant involvement of medications in accidents is demonstrated in FMCSA's *Large Truck Crash Causation Study* (Craft et al. 2007). In that study, prescription and OTC drug use were considered "accident associated factors" in 26% and 17%, respectively, of the 967 accidents. (An accident associated factor was defined by the study authors as a "factor that could be important," not the "critical reason" or "event" causing the crash.)

Further importance of the involvement of medications in highway accidents is provided by research conducted on Australian truck drivers in a volunteer study published in 2004 (Howard et al. 2004). In this study, drivers who consumed benzodiazepine-type medications were found to be 1.91 times more likely to have had a crash in the previous 3 years, 3.44 times more likely to have crashed with use of antihistamines, 2.4 times more likely to have crashed with use of narcotic analgesics, and after consuming alcoholic drinks, only 1.09 times more likely to crash. They were no more or less likely to have crashed if they consumed stimulant drugs such as caffeine (Howard et al. 2004).

Commercial truck and bus/motorcoach drivers are required by law to undergo medical evaluation on a periodic basis (with no longer than 2 years between examinations) to be permitted to drive or to continue driving commercial vehicles (49 CFR 391.11). The public and drivers' employers rely on medical practitioners in the conduct of Commercial Driver Medical Examinations (CDMEs) to ascertain whether an individual driver meets the standards of applicable federal safety rules (49 CFR 391.41) . . . that the driver has no "established medical history of clinical diagnosis of" . . . a medical condition . . . "likely to interfere with the safe operation of a commercial motor vehicle."

The medical examiner role in evaluating and advising drivers on use of medications was detailed in the FMSCA-sponsored "Role Delineation Study." This was a methodologically and statistically robust detailed study of the medical examiner role in providing CDMEs. The study was conducted between 2005 and 2007 and it reported on 2,297 surveyed medical examiners of commercial drivers within each of the designated professions performing these examinations (medical doctors, doctors of osteopathy, chiropractors, physician's assistants, and advanced practice nurses.)

Tasks associated with the performance of CDMEs were identified and their importance was assessed; the knowledge, skills, and abilities required to perform those tasks were also identified so as to facilitate examiner training and testing in connection with the development of a proposed National Registry of Certified Medical Examiners (NRCME). Of the 146 tasks performed by medical examiners during the examinations of commercial drivers, five medication-related tasks were identified. Each was given high importance by the examiners (3.71–3.91/4), and study participants (89%–98%) indicated they performed those tasks for almost all commercial driver examinations completed.

A number of sources for medical examiner guidance on the potential effect of medications on commercial driver safety have been published by the FMCSA. These include rules prohibiting use of insulin [391.41(b) 3] and controlled substances [391.41(b)12] and advisory guidelines including frequently asked questions (FAQs) on the FMCSA Medical Program Web Page, medical conference reports, evidence guidelines, and medical expert panel reports, as well as the NRCME *Medical Examiner Handbook.* In addition, the Medical Review Board of the FMCSA commented extensively on medication use and made recommendations to the FMCSA. All of these documents have been published by the FMCSA, are available for public access on the FMCSA website, and can be used to assist medical examiners in determining whether drivers who admitted taking certain medications would be able to drive safely. Each of these sources are in separate web locations, are organized by disease entity, and, for the most part, cover medications in the context of the specific diseases. This information is rapidly changing, with many of these sources being published during the development of this synthesis report. See the FMCSA website for details and the status of each. Review of these sources of information for the medical examiner is beyond the scope of this synthesis.

Medications rather than *medical conditions* were chosen to be queried for this synthesis survey, because the common uses of many of the medications are "off-label," which means being prescribed for reasons not approved by the FDA for use in treating a specific disease. Once a medication is on the market for one indication (disease), "the FDA has a limited role in governing use of that medication for other clinical indications." It is both legal and common for medical providers to prescribe medication for off-label uses based on their judgment that the patient will benefit. According to published reports, up to 21% of prescriptions in the United States are written for off-label use (Stafford 2008). Common examples include the use of trazodone, an antidepressant, for insomnia, wherein it is approved for use only as an antidepressant; or gabapentin, a seizure medication, which is also commonly prescribed for diabetic neuropathy and for the movement disorder of restless legs syndrome (Stafford 2008; Krystal 2009).

The examiner must rely on the driver to accurately and completely list his or her medications, and may rely on reporting by the driver's prescribing physician on medication effect, make his or her own assessment of medications reported, or do both (FMCSA FAQ #77 "What medications disqualify a CMV Driver").

MEDICAL EXAMINER SURVEY REGARDING MEDICATIONS USED BY COMMERCIAL VEHICLE DRIVERS

Aims of the Survey of Medical Examiners

In light of the availability of information from the FMCSA regarding the specific medications, and the recognized role and importance of medical examiner efforts in evaluating driver medication use, in this convenience sample survey an attempt was made to characterize what decisions CDMEs anticipate they would make when faced with the decision of whether to "qualify or not to qualify" a commercial driver for their required medical examiners certificate based on issues concerning medications the driver may be taking.

In this survey, the synthesis team aimed to answer the following questions:

1. What are medical examiners' knowledge, understanding, and actions in qualifying commercial drivers with admitted Schedule II medication use under the FMCSA rules and guidelines?
2. Are examiners providing certification in accordance with published FMCSA rules and guidelines with respect to Schedule II medications? To what extent do they vary from those rules and guidelines?
3. Is there awareness of potential hazards of medications such that examiners require additional steps for the driver to qualify?
4. Is there agreement among medical examiners about which medications drivers would admit taking that would still permit them to be medically certified to continue driving?
5. To what extent are medical examiners providing drivers with guidance on the safe use of medications?
6. To what extent are medical examiners routinely providing employers with Department of Transportation DOT Long Form (Form 649-F-6045): Medical Examination Report for Commercial Driver Fitness Determination? To what extent are they communicating (with or without the driver's granted release of personal information) regarding specific certification issues or medications in commercial drivers examined at their behest, or do they provide employers with lists of prohibited drugs/medications?

Medical Examiner Survey Participants

In 2008, a questionnaire was administered to two small groups of medical examiners of commercial drivers. Twenty-three examiners were surveyed at two educational meetings of practicing occupational medicine specialists in two locations: 8 in Reno, Nevada, and 15 in Salt Lake City, Utah.

Of the 16 forms distributed on September 11, 2008, to a Salt Lake City group of occupational medicine clinic providers, 15 were completed and returned. This first survey group included 12 practicing occupational medicine physicians, including 3 occupational medicine residents, and 3 mid-level practitioners (Advanced Practice Registered Nurses), who were primarily working in occupational health clinics in Utah. A number of additional questionnaires were sent by e-mail to those who could not attend, but no additional completed surveys were received. Completed survey forms were scored in paper form.

Eight questionnaires were distributed and returned by physicians who attended a lecture given by Dr. Howard Leaman at Reno, Nevada, on November 12, 2008. The surveys were all returned before the talk began. Four physicians were employed in private practice and reported seeing commercial drivers in their practice, two practiced in occupational medicine clinics, one was an urgent care physician, and one was a corporate physician. Five of the 8 physicians were certified in a medical specialty: family practice or cardiovascular disease. None were certified in occupational medicine. The average number of department of transportation (DOT) exams (CDME) per week was 4, with a range from 0 to 20 exams per medical provider. Some demographic information about the respondents in the two groups is depicted in Table 5.

Surveys were conducted anonymously so that responses were protected and treated confidentially, and the responses could not be identified with any particular respondent. The responses on the completed questionnaires were hand-scored and entered into an Excel spreadsheet for tabulation of the results. Only statistical measures of central tendency are

TABLE 5
PARTICIPANTS IN SURVEY QUESTIONNAIRE ASKED OF MEDICAL PROVIDERS OF COMMERCIAL DRIVER MEDICAL EXAMINATIONS

Survey Participants on Commercial Driver Examinations			
Variables	Reno, Nevada	Salt Lake City, Utah	Group
Number of Participants	8	15	23
Average Age	49	48	48.5
Male/Female	0.80	0.63	0.71
MD/Mid-level Practitioner (APRN)	1.00	0.80	0.90
Percent MD Board Certified	0.38	1.00	0.62
CDME Average (number per week)	4.00	17.00	10.00
Range	0–20	0–35	<0–35
Providers Reporting Their Practice Is Primarily Occupational Medicine	0.25	0.80	

reported here; no particular parametric statistical analyses are provided because of the limited group size.

Because of the small number of respondents, one cannot infer that the responses of those surveyed are representative of the opinions of all medical examiners of commercial drivers. That is particularly relevant in view of the coming requirement that examiners must be qualified by examination and registered to perform medical certification examinations for drivers. Nonetheless, the survey responses here provide insight into the decision-making process in two groups of individual CDMEs responsible for the medical qualification of commercial drivers.

These survey data represent an initial look at medical provider decision making regarding driver medications in the CDME certification process. The survey results may prompt further investigation using larger groups, better selected medication lists, and statistical methods for improving validity and inference to the larger population of medical examiners.

In the several literature searches performed for this synthesis study, including that of the PubMed National Library of Medicine Search Engine, no published reports were identified that provided this specific information.

MEDICATIONS AND MEDICATION CLASSES

Introduction

The medications chosen for survey were identified by synthesis co-author (Leaman) based on NTSB accident reports and on personal experience performing commercial driver certification examinations over a 25-year career in occupational medicine.

The first group of medical providers, surveyed at Salt Lake City, Utah, was presented with a list of 69 drugs and medications, grouped into 12 categories. Some of the more commonly available pharmaceuticals were identified by their trade name so as to ensure that the respondents knew the medications by their recognizable names. However, in reviewing responses from the Salt Lake City group, it became apparent that several medical providers lacked familiarity with some of the 69 medications listed. Consequently, the number of medications queried of the Reno, Nevada, group was reduced to 52 medications in 10 categories, which helped limit the amount of time required to respond to the lengthy questionnaire. The complete list of 69 drugs is described in subsequent sections, with annotations to indicate which 17 were deleted from the second set of questionnaires before administration to the Reno group. The average medical provider took 20 to 25 min to complete the questionnaire in both locations (Salt Lake City and Reno).

The medical examiners were asked to classify each medication by the actions they would normally take when presented with that medication by a commercial driver at the time of his/her CDME.

On the examiner survey, the medications were grouped into functional categories. Results were expressed as proportions rather than percentages to avoid the appearance of statistical validity or inference that this group represents all medical examiners. This was a very small sample size ($n = 23$), and the results cannot be said to represent all CDM examiners.

For each medication listed, survey participants were given the opportunity to choose one or multiple options to indicate either how they have previously handled such questions, or would handle them now, at the time of the survey administration (2008):

Response options to medications listed in the Medical Examiner survey:

Option 1: Never approve
Option 2: Approve (only with note from treating MD)
Option 3: Approve with objective testing
Option 4: Approve with detailed history from driver
Option 5: Approve only if prescription meds are taken 8 hours or more before driving
Option 6: Usually/always approve
Option 7: I do not ever see this drug
Option 8: I am not familiar with this drug

Definitions:

Issuance: Granting of a medical certificate to a commercial driver from an appropriately designated medical examiner for any period of time.

Conditional issuance: Granting of a certificate to a commercial driver by an appropriately designated medical examiner, pending the driver's agreeing to comply with a condition of issuance such as providing the examiner with a note from the prescribing practitioner, providing additional detailed medical history at the time of the examination, additional objective testing, and/or medical certification with the stipulation that the medication in question be taken 8 h or more before driving.

No issuance: Driver is not issued a medical certificate at the time of the examination.

Pain Medications

Tramadol (*Ultram®*)
Oxycodone (*Oxycontin®*)
Oxycodone (*Percocet®, Lortab®*)
Codeine (*Tylenol with Codeine*)
Morphine (*Kadian®*)
Methadone (*Dolophine®*)

Applicable FMCSA Regulation and Guidance regarding controlled substances:

Federal Rule 391.41(b)(12):

A person is physically qualified to drive a commercial vehicle if that person:

Does not use a controlled substance identified in 21 CFR 1308.11, Schedule I, an amphetamine, a narcotic, or any other habit-forming drug.

Exception: A driver may use such a substance or drug, if the substance or drug is prescribed by a licensed medical practitioner who is familiar with the driver's medical history and assigned duties; and has advised the driver that the prescribed substance or drug will not adversely affect the driver's ability to safely operate a commercial motor vehicle.

This exception does not apply to the use of methadone.

The intent of the medical certification process is to medically evaluate a driver to ensure that he or she has no medical condition that interferes with the safe performance of driving tasks on a public road. If a driver uses a Schedule I drug or other substance, an amphetamine, a narcotic, or any other habit-forming drug, it may be cause for the driver to be found medically unqualified. Motor carriers are encouraged to obtain a medical practitioner's written statement about the effects on transportation safety of the use of a particular drug.

A test for controlled substances is not required as part of this biennial medical certification process. The FMCSA or the driver's employer should be contacted directly for information on controlled substances and alcohol testing under Part 382 of the Federal Motor Carrier Safety Regulations.

The term "uses" is meant to encompass instances of prohibited drug use determined by a physician through established medical means, which may or may not involve body fluid testing. If body fluid testing takes place, positive test results should be confirmed by a second test of greater specificity. The term "habit forming" is intended to include any drug or medication generally recognized as capable of becoming habitual, and that may impair the user's ability to operate a CMV safely. The driver is medically unqualified for the duration of the prohibited drug(s) use and until a second examination shows the driver is free from the prohibited drug(s) use. Re-certification may involve a substance abuse evaluation, the successful completion of a drug rehabilitation program, and a negative drug test result. Additionally, given that the certification period is normally two years, the medical examiner has the option to certify for a period of less than two years if this examiner determines more frequent monitoring is required. (See Conference on Neurological Disorders and Commercial Drivers and Conference on Psychiatric Disorders and Commercial Drivers at: http://www.fmcsa.dot.gov/facts-research/research-technology/publications/medreports.htm.)

Survey Results (Pain Medications)

Methadone Commercial drivers are prohibited from driving while taking methadone, and medical certification for commercial driving is also not permitted [391.41(b)(12)].

Thirteen of the 23 medical examiners surveyed correctly identified this rule in the questionnaire and indicated the driver would "Never" be issued a certificate while taking that medication. Unfortunately, eight medical examiners did not, with five indicating they would provide medical certification when presented with a note from the driver's prescribing physician; two would approve if provided with a detailed history taken in the clinic; and one if the driver took the medication 8 h or more before driving. There were differences between locations, with only one of the eight Reno providers surveyed indicating "no certificate" would be issued; the others would provide certification conditioned on receipt of the prescribing physician's note, completion of a detailed history in the clinic, or results of some objective testing.

Other opiates There appeared to be regional differences in conditional approvals for opiates, most notably methadone, followed by oxycodone (Oxycontin®) and morphine (Kadian®). These are potent opiate medications usually prescribed for severe chronic pain. For oxycodone (Oxycontin®), 8 of the 23 surveyed providers would not anticipate providing a medical certificate to a driver who admitted taking this medication; 7 would require a physician's note; and 5 would instruct

the driver to take the medicine 8 h before driving. For morphine (Kadian®), 8 of 23 surveyed providers indicated they would never qualify a commercial driver admitting to use of this drug. Of the others who would conditionally allow medical certification, 6 of 23 would require a physician's note, 4 of 23 a detailed history in clinic, and 4 of 23 indicated advising the driver to take the medication no sooner than 8 h before driving. For Tylenol with codeine, most indicated they would qualify a driver with a note from their prescriber in 6 of 23 examiners, detailed history in 10 of 23 surveyed examiners, and instructions by 11 of 23 examiners to take the medication no sooner than 8 h before driving.

Tramadol Drivers admitting use of this medication were anticipated to be in a medically certified condition on providing a detailed medical history to the examiner in the clinic by 13 of the 23 examiners. Six of 23 examiners indicated the driver would be qualified, and the driver was instructed to take the medication no sooner than 8 h before driving.

Summary (Pain Medications)

Methadone Substantial variation existed between the two groups of medical providers surveyed (Reno and Salt Lake City groups) in terms of providing medical certification to drivers who admit taking the drug methadone, which is specifically regulated (prohibited) in FMCSA rules 391.41(b)(12). Some providers of CDMEs are apparently unaware, or for some reason do not comply with the DOT regulation stating that this medication is prohibited for use in commercial driving.

Regional differences appeared with respect to permitting drivers to be certified when taking methadone: most of the Reno group of providers reported they would issue conditional certificates to drivers, whereas in the Salt Lake City group only 3 of 15 medical examiners would permit conditional certification for drivers who admit to methadone use.

Other Opiate/Pain Medications (*not methadone*) Questionnaire responses showed consistency for the opiates/pain medications, particularly regarding tramadol, where all of the medical providers responded they would permit conditional or full certificate issuance to drivers who admitted taking it. Of the 23 providers surveyed, only 3 would require a driver's prescribing physician statement in compliance with 391.41(b)(12) before issuing a certificate for a driver taking tramadol (Ultram®). Over all the pain medications, only 6 of 17 respondents who would allow certification stated they would require the prescribing physician's written statement before issuing a medical certificate to a commercial driver.

There was uniform response on "would issue" a certificate (conditional or "usually always") for oxycodone (Percocet®, Lortab®) (21 of 23) and codeine (Tylenol with codeine) (22 of 23). There were substantial inter-group or regional differences in the willingness to issue a certificate to a driver who admitted taking oxycodone (Oxycontin®) (Salt Lake City: 8 of 15; Reno: 3 of 4 respondents who answered) and issuing a certificate for a driver who admitted taking morphine (Kadian®) (Salt Lake City: 7 of 15 respondents; Reno: 4 of 6 who responded).

Stimulant Medications

d-Amphetamine (*Adderall®*)
Methylphenidate (*Ritalin®*, *Concerta®*)
Modafinil (*Provigil®*)
Caffeine (*No Doze®*, *Vivarin®*, etc.)
Energy drinks (*Red Bull®*, etc.)

Survey Results (Stimulant Medications)

D-Amphetamine Conditional medical certification was anticipated by 14 of 23 surveyed examiners when presented with a driver who admits taking amphetamine, most often conditioned on receiving a treating physician's note (7 of 23) and in 3 of 23 instances a detailed medical history in the clinic. Six of the 23 examiners indicated that they would never medically qualify a driver who admits to taking amphetamine, and 2 of 23 marked "Usually always" qualifying such a driver. Several of the examiners indicated they never see this medication in their practice with commercial drivers. Compliance with 391.41(b)(12) was similar between regions for those who would issue the certificate [Salt Lake City (6 of 11); Reno (3 of 6)].

For the other prescription stimulants such as methylphenidate (e.g., Ritalin®), the majority of the medical providers would certify drivers using these medications if a detailed history in clinic and a physician prescriber's written statement were provided. No providers indicated they would "Never" qualify a driver using methylphenidate, 13 of 23 would require the prescriber's written statement, and 7 of 23 would require additional detailed history in the clinic. Modafinil (Provigil®) was "Usually/Always" approved by 4 of the 23 medical providers surveyed, with an additional 8 of the 23 providers indicating they would require a prescriber's written statement, and 8 requiring a detailed history in the clinic.

A question concerning drivers admitting to the use of caffeine and energy drinks was marked "Usually/Always" permitted certification in 6 and 7 of the providers, respectively, with the majority, 9 and 10 of 23 providers, indicating they would require a detailed history in the clinic for these drivers. Curiously, two providers indicated they would "Never" issue a medical certificate to drivers ingesting these substances.

In summary, for the small group surveyed, there were regional differences (Reno vs. Salt Lake City) and variation in anticipated practice among providers. The source of this variation was not identified in the data; however, data from another part of the questionnaire may be relevant.

Antidepressants and Other Psychiatric Medications

Psychotropic Medications

Selective Serotonin Reuptake Inhibitors (SSRIs)
Venlafaxine (*Effexor*®)
Fluoxetine (*Prozac*®)
Sertraline (*Zoloft*®, etc.)
Atomoxetine (*Straterra*®)
Bupropion (*Wellbutrin*®)
Mirtazapine (*Remeron*® and other heterocyclic antidepressants)
Tranylcypromine [*Parnate*® (MAO Inhibitor)]
Amitriptyline (*Elavil*®)
Lithium (*Eskalith*®)
Quetiapine (*Seroquel*®)
Abilify/Geodon (deleted for the 2nd round of questionnaires)

Survey Results (Psychotropic Medications)

For SSRI-type antidepressants, 14 of 23 surveyed medical examiners would qualify drivers with additional history in clinic; only 2 of 23 indicated that they would require a written statement from the provider who prescribed the driver's antidepressant.

In the surveyed group, no examiners indicated they would "Never" qualify a driver who admitted taking any of the medications queried. Other than lithium, conditional approval was the most common response, with detailed history in clinic required for most medications queried. In the case of lithium, 13 of 23 medical examiners would require the driver to provide a written statement from their prescribing physician.

Quetiapine (*Seroquel*®—a member of a class of medications known as atypical antipsychotics) and amitriptyline (*Elavil*®) and mirtazapine (*Remeron*®) (sedating antidepressants), were the only medications in this class where examiners anticipated advising the driver to take the medication no sooner than 8 h before driving. Unfortunately, this was not prevalent, and only 3 of 23 examiners indicated no driving sooner than 8 h after use of amitriptyline medication, and 2 of 23 indicated this for mirtazapine (*Remeron*®) or Quetiapine (*Seroquel*®).

Antihistamines

Diphenhydramine (*Benadryl*®)
Hydroxyzine (*Atarax*®)
Loratadine (*Claritin*®)
Monoleukast (*Singulair*®)
Astemizole (*Hismanal*®)
Cetirizine (*Zyrtec*®)

Survey Results (Antihistamines)

The most commonly occurring response from the medical examiners in this drug category was "Approve only if medication taken 8 h or more prior to driving." The number of the examiners indicating no medication use within 8 h of driving included: diphenhydramine (Benadryl®) 17 of 23; hydroxyzine (Atarax) 12 of 23; and certirizine (Zyrtec) 10 of 23. There appeared to be little regional variation in these recommendations. Of those surveyed, only one provider of the 23 indicated that he/she would "Never" certify a driver taking diphenhydramine (Benadryl®) or hydroxyzine (Atarax).

Neuroleptic Medications

Gabapentin (*Neurontin*®)
Pregabalin (*Lyrica*®)
Dilantin
Phenobarbital
Lamotrigine (*Lamictal*®)
(*Keppra*®) (deleted in 2nd questionnaire)

Survey Results (Neuroleptic Medications)

The surveyed examiners consistently indicated conditional approval for gabapentin (Neurontin®) and pregabalin (Lyrica®). For gabapentin (Neurontin®), 18 of the 23 surveyed examiners would provide conditional approval, with 11 requiring that the driver provide additional detailed history in clinic, 4 requiring that the driver provide a note from the prescribing physician, and 2 would instruct the driver to take the medication 8 or more hours before driving. For dilantin, typically used for seizure control and sometimes peripheral neuropathy, the response was different, and varied by location. Eight of the 23 examiners indicated they would "Never" medically qualify a driver taking this medication; most of these examiners were in Salt Lake City. In Reno, four of the eight surveyed practitioners indicated they would require a physician's note. To either effect, the examiners appear to be further inquiring why the medication is being used (seizures, neuropathy, or some other reason). The FMCSA specifically states that, "Use of medication to prevent seizures is disqualifying" (FAQ #77). Similar to their responses to dilantin, medical examiners evaluating drivers admitting use of phenobarbital either would never qualify the driver (8 of 23) or would require the driver to present a prescribing physician note (6 of 23). Lamotrigine (*Lamictal*®) is a neuroleptic agent, typically used as a mood stabilizer in bipolar disorder. Twelve of the 23 medical providers either would never qualify a driver who admitted to taking this medication or would require the driver to present a medical note before considering qualification for a commercial driver medical certificate. Four of the 23 surveyed would "approve," conditioned on a detailed history in the clinic, and five examiners indicated that they never see this medication.

Sedatives and Hypnotics

Lorazepam (*Ativan®*)
Clonazepam (*Klonopin®*)
Diazepam (*Valium®*)
Temazepam (*Restoril®*)
Flurazepam (*Dalmane®*)
Buspirone (*Buspar®*)
Zolpidem (*Ambien®*)
Eszopiclone (*Lunesta®*)
Trazodone (*Desyrel®*)
Melatonin

Survey Results (Sedatives and Hypnotics)

Lorazepam (Ativan®), clonazepam (Klonopin®), and diazepam (Valium®) have significantly different half-lives affecting the time impairment may potentially last after a dose is taken. These were deliberately placed side-by-side in the questionnaire to identify whether half-lives were a consideration in medical examiner decision making. Similarly, the hypnotic medications, also of widely varying half-lives, were placed side-by-side to identify differences in examiner anticipated actions.

In the group surveyed, examiners indicated they would conditionally certify, and not automatically qualify or disqualify, drivers who admitted taking these medications. This was consistent between both groups of examiners (Salt Lake City and Reno). The majority of the responses indicated examiners instructing drivers not to drive within 8 h of taking the medication (9 to 14 of 23). Fewer examiners would insist on a note from the driver's prescriber (4 to 7 of 23). Hypnotics zolpidem (Ambien®) and eszopiclone (Lunesta®) had the most providers advising taking the medication at least 8 h before driving (14 of 23 for both); temazepam (Restoril®) the next highest (12 of 23); and, lorazepam (Ativan®), clonazepam (Klonpin®), and diazepam (Valium®) and flurazepam (Dalmane®) had similar numbers of examiners indicating they would qualify the driver if he/she took their medication no sooner than 8 h before driving (9 to 10 of 23).

Dopamine Agonists

Pramipexole (*Mirapex®*)
Ropinirole (*Requip®*)
Levodopa–Carbidopa (*Synemet®*)
Levodopa–Carbidopa–Entacapone (*Stalevo®*)
(deleted in 2nd questionnaire)

Survey Results (Dopamine Agonists)

The medical examiners were also asked about pramipexole (Mirapex®) and ropinirole (Requip®). Twelve and 13 of the 23 respondents indicated they would approve a driver presenting for certification with either of these medications. A prescribing physician's note, detailed history in clinic, and instructions to take the medication no sooner than 8 h before driving were the conditions of certification. Two of 23 examiners indicated they would "Never" qualify, and 2 others indicated they "Usually/always" qualify commercial drivers who admitted taking these medications. Six of the 23 indicated they "Never see" these medications.

Levodopa/carbidopa (Synemet®) provoked 10 of the 23 examiners to mark "request a prescribing physicians note"; 4 of 23 indicated they would "Never" qualify a commercial driver taking this medication; and 2 of 23 indicated that they "Usually/always" qualify a commercial driver who admits to using this medication.

Cardiac Medications and Drugs for Heart Conditions

Dobutamine (*Dobutrex®*)
Amiodarone (*Cordarone®*)
Digitalis

Survey Results (Cardiac and Heart Medications)

The medical examiners response to dobutamine (Dobutrex®) indicated that this medication is not commonly observed. Six of 23 medical examiners reported they "Never" see this medication in commercial driver certification examinations. Sixteen medical examiners indicated they would conditionally approve a driver if they were to submit a prescribing physician note, provide a detailed medical history, and undergo objective testing. Only two medical providers indicated they would "Never qualify" an individual who admitted to using dobutamine.

Three of 23 examiners indicated they would "Never" qualify a driver who admitted taking amidarone (Cordarone®); 4 would require a detailed history in the clinic, 2 objective testing, and 11 of 23 would require a note from the treating physician.

For digitalis, 17 of the 23 surveyed examiners indicated they would conditionally approve drivers taking this medication, with 4 of 23 indicating "Usually/Always." A physician note (11 of 23), detailed medical history in the clinic (4 of 23), and requiring objective testing (2 of 23) were the conditions specified for certification of drivers admitting taking digitalis.

Other Medications and Commercial Drivers

Varenicline (*Chantix®*)
Theophylline (deleted in 2nd questionnaire)
Prochlorperazine (*Compazine®*)
(deleted in 2nd questionnaire)
Diphenoxylate and atropine (*Lomotil ®*)
(deleted in 2nd questionnaire)

Survey Results (Other Medications)

For varinicline (Chantix®), 8 of 23 medical examiners indicated they would "Never" medically certify a driver of commercial vehicles who admitted taking this medication. Four of the 23 indicated conditional approval pending the receipt of a detailed medical history, and one respondent, "only if the driver took the medication no sooner than 8 h prior to driving." There were significant regional differences, with 5 of 8 examiners in Reno indicating they would "Usually/Always" certify and only 1 of the 15 Salt Lake examiners indicating so.

Educating Drivers About Medications

The medical examiner survey participants were asked whether or not they engaged the commercial drivers they were examining in discussions to "educate them" about medications or drugs of any kind, or even to discuss nutritional supplements and their possible effects on driving performance.

Q: What "education or training" (guidance, information pamphlets, etc.) do you usually give to commercial drivers regarding any medications?
Please answer the question above whether the driver admits to self-medicating, or regarding the drug prescriptions you are giving them as a part of treatment you recommend or monitor with your patient?
__ None, __ "Driving caution" on prescription written for driver,
__ Other material: list below

Responses:

Driver Education on Medications by Medical Providers during the Commercial Driver Medical Evaluation

	Salt Lake	Reno	Combined
No Education	1/15	1/8	2/23
Driving Caution	9/15	4/8	13/23
Other	2/15	1/8	3/23

Verbatim responses (other material): "Verbal guidance," three examiners, one each: "Never use sedating meds within 8 hours of driving"; "No driving on narcotics, sleeping meds"; and "Can't use benzodiazepines within 8 hours of driving."

Conclusion on advice to drivers on safe medication use: In this small survey, the education of commercial drivers about medications is most often limited to "Driving caution" on prescriptions written by only some medical examiners who as part of their own medical practice are also providing medical care to commercial drivers (8 of 23). "Verbal guidance" is given by very few providers regarding medication use (8 of 23). Driver guidance appears to be limited to the restriction of medication use to 8 h before working (driving).

Interactions with Drivers' Employers (e.g., carriers)

Q: Do you provide a list of prohibited drugs for commercial drivers to employers?
___ Yes ___ No
If Yes, what is the source of the list?
_____

No medical examiners surveyed indicated that they provide any list of medications to employers with whom they work. The only published list of medications mentioned by the providers was that by Airline Owners and Pilots Association (AOPA).

Q: Do employers require the "long form" medical examiners report?
____ yes, most of the time _____ no, not usually

Percent of Medical Examiners Reporting Employers Require the DOT "Long Form" from them after Medical Examination of Commercial Drivers

	Salt Lake	Reno	Combined
Long Form Required	10/15	2/8	12/23
Long Form Not Required	5/15	6/8	11/23

Summary of employers requiring DOT Long Form. The "DOT Long Form" (Form 649-F-6045) containing a driver's personal medical history, physical examination, and examiner's certification decision is required by employers in some but not all geographic regions. Factors influencing this are not clear, and there was considerable variability within the two regions surveyed (Salt Lake City and Reno).

Q: What interactions do you usually have with drivers' employer over issues of prescribed medications for their drivers?

Medical Examiners reporting Employer Communication on Driver's Specific Medication

	Salt Lake	Reno	Combined
Employer Interaction	6/15	0/8	6/23
No Employer Interaction	9/15	8/8	17/23

Responses: Salt Lake City—Verbatim responses given by medical examiners:
"usually none, if concerned will call and talk to employer about driving on meds"
"inform them if disqualified"
"very limited"
"hardly have any, but if [we] do, usually [it's] about narcotics"
"phone call"
"usually I am justifying to the employer why I am concerned about a driver's meds and educating them on safety issues."

Responses: Reno:

None of medical examiners surveyed indicated that they interact with employers regarding specific medications.

Summary of medical examiner interaction with employer on driver's prescribed medication. In this small survey, the medical examiners appeared to vary by region on whether they interacted with drivers' employers on specific medications taken by their drivers (employees). Verbatim responses indicated that medical examiner interaction with drivers' employers is very limited, often only to justify reasons for disqualification or providing information on a driver related to his or her operating safety and often specifically regarding narcotic medications.

Percent of Medical Examiners Reporting Company Official Interaction Regarding Specific Drivers

	Salt Lake	Reno	Combined
Employer Interaction	9/15	1/8	10/23
No Employer Interaction	5/15	7/8	12/23

Q: Do you interact with company officials regarding specific patients (drivers)?
___ Yes ___No

Verbatim responses given by medical examiners included:

"inform if not qualified, and give reasons"
"pass or no pass"
"exam status (pass no pass, awaiting info)"
"medical condition likely will not interfere with obtaining medical certification, or inform about outright rejection in general terms if personal"
"warn if going elsewhere for medical card"
"address driving safety issues, physician follow-up required"
"justify concerns regarding medications and safety—educate regarding general DOT policy"
"without releasing specific information; e.g., common sedating meds, common side effects are."

Q: What information do you give without a written release of information?
___None, __other, note below:

Responses: Salt Lake City

Employer interactions: two medical examiners surveyed did not give employers information about driver physicals without release of information.

Verbatim responses on specific information given by medical examiners included:

"always require written release of information"
"driving safety issues, inform if not qualified, and reason"
"basic information: pass or no pass, if Personal Medical Doctor follow up required"
"justify concerns regarding medications and safety—educate about general DOT policy"
"without a release, I educate in general terms . . . ; e.g., the DOT policy is . . . Common sedating medications are . . . common side effects of medicine x are . . ."
"hardly ever"
"reason why card not issued"
"1 or 2 responses concerned elderly drivers, only give out information that pertains to driving safety"
"if concerned, I will call and talk to employer about driving on medications . . . especially if concerned about circumventing not receiving card by going elsewhere for card"

Responses: Reno: No information was reported given without a release form.

Summary of medical examiner release of information to driver's employer: After completing the driver's medical examination (CDME), regional variation on information release to employers was identified in the small group of medical examiners surveyed. This was the case for both medication issues as well as examination issues. In Salt Lake City, 6 of the 15 medical examiners did report interacting with the drivers' employers, whereas in Reno none of medical examiners reported interacting with employers.

When verbatim responses were examined, it became evident that the medical information reportedly given by 6 of the 15 members of the Salt Lake group related to work fitness or issues regarding medications that the employer will likely learn from the Medical Review Officer (MRO) in drug testing notification under 49 CFR Part 40.21 (Provision for "Stand Down").

Q: Do you provide a list of prohibited drugs for commercial drivers to employers?
___ Yes ___No

Responses: Salt Lake City and Reno

No medical examiners indicated they provide a drug list to employers for the purpose of determining which medications are "safe" or "approved," although one mentioned the FAA list and the Airline Owners and Pilots Association (AOPA) pamphlets as general guidelines.

Questions about Alertness Management

Q: Do you routinely advise drivers on how to maintain alertness and combat fatigue?
___ Yes ___No

Responses:
Only two of the medical examiners surveyed (at Salt Lake City) reported giving alertness advice to drivers at the time of their examination. One reported discussing sleep hygiene; the other discusses sleep apnea risk and referral. The remaining 21 medical examiners reported that they do not give drivers advice on "remaining alert and combating fatigue."

Q: What do you tell them? (No responses)

Examiners' Comments and Suggestions to Open-Ended Question

The end of the questionnaire/survey forms allowed the medical providers (examiners) an open-ended opportunity to provide their comments and suggestions.

Q: Your Comments and Suggestions here: Here we solicit your comments, suggestions, recommendations, etc., concerning the medical examining process and/or the Medical Qualification Standards for CMV drivers. Remember these comments will be held in confidence, so please be frank, but also be specific enough that we can determine precisely what your comments mean in the context of this synthesis study.

Verbatim responses to open-ended question: Only a small number of open-ended responses were received, among them the following specific comments were proffered:

"Indication for Rx [underlying condition being treated] plays a large role in how I handle different cases."

"Priority needs to be national standards/certification for providers; need a national database for drivers so they cannot MD shop."

"I am not familiar with the Hartenbaum book."

DISCUSSION OF SURVEYS OF MEDICAL EXAMINERS

This Survey

This survey of a small number of medical examiners ($n = 23$) of commercial drivers found the following:

- There was some variation in responses of the group of medical examiners surveyed on whether their anticipated actions adhered to published federal rules with respect to methadone and Schedule II medications.
- There also appeared to be variation in medical examiner anticipated actions regarding medications that had no specific rules associated with their use. The examiners were queried about a large number of medications. Other than methadone, these medical advisors would permit most of these medications for use by commercial drivers on the condition of receiving the prescribing physician's release notes, or by giving the driver advice to take medication no sooner than 8 h before driving, or by completion of a detailed evaluation at the clinic.
- The amount of education about medications provided to drivers by their CDME examiners was limited in this small group of surveyed examiners. The most common advice was to avoid the of use of a medication within 8 h before work; advice most commonly given when the medical examiner prescribes medications to the drivers for medical conditions for which they are providing care.
- According to the group surveyed, the Medical Examination Report (Form 649-F-6045) is required by some employers in addition to the Medical Certificate. This appears to vary by region.
- Medical examiners' interactions with employers without specific release of information were reported in about half of the Salt Lake City group, and by none of the Reno group. Information released was cited as primarily related to safety concerns, or why the driver did not "pass" the examination.
- The group of examiners surveyed reported that they very seldom provided *alertness education* to drivers they examined. Of the 2 of 23 examiners who indicated they provide such education, one reported discussion of "sleep hygiene" and the other "sleep apnea."
- Medical examiners surveyed were not aware of any "list" of prohibited medications.
- Open-ended responses by medical examiners were limited, and emphasized a need for a national medical examiner standard of performance and the need to know underlying conditions (why the medication is being prescribed). One of the examiners indicated that he or she was not familiar with one of the more commonly used privately developed sources of information on the CDME (Hartenbaum 2006).

This initial study survey was limited by a number of factors:

1. The size of the surveyed group (23 participants). The U.S.DOT's FMCSA estimated that there are 317,000 medical providers who might perform driver physical examinations on a regular basis in the United States (FMCSA NPRM, 73FR-73129, 1 Dec. 2008); however, in the synthesis survey work reported here, only 23 of these medical examiners in two western cities were questioned. Therefore, these survey data, on so few medical professionals, cannot provide any inferences about the activities of so many other medical examiners. Nonetheless, this survey provides insight into

practices "in-the-field," and these data help underscore the need to extend such survey work to other groups of CDME examiners.

2. The list of medications queried was not a complete list of all medications used by drivers of CMVs. Medications were chosen by the synthesis co-author (H. Leaman) based on his experience, review of NTSB accident reports, and personal observations made during a 25-year occupational medicine practice. This survey study could be expanded and strengthened by better methodology, including methods for choosing medications.

Observations Made from Survey Results

One of the more significant limitations on the process of medical examiners performing evaluations of commercial drivers (CDME) includes the completeness, or incompleteness, of driver self-reporting of their medications to the medical examiner. Although drivers are required to complete their medical history form accurately and completely (or risk invalidating their certificate) there is evidence this does not always happen; numerous medical examiners attest to this from prior experiences with drivers who deliberately disguise the truth on their personal history forms and in interviews at the time of CDME exams.

Estimate of Foreseeable Risk

One key issue that is implied but not explicit in this survey is that the certification actions of the medical providers represent their "estimation of foreseeable risk" of motor vehicle accidents in the commercial drivers they examine. In the *Medical Examiners Handbook* (NCRME-FMCSA) the recommendation is given to certify the driver "if the examiner believes that the nature and severity of the underlying condition does not interfere with safe driving and the effects of medication use while operating a commercial motor vehicle does not endanger the safety of the driver and the public."

Lack of Common Reference Guidance

Two possible sources of CDME certification decision variability regarding safe medication use that were encountered in this study are: (1) the absence of a commonly accepted, single source, up-to-date, medication-based (rather than disease based) reference guideline ("List") for use by CDME in the certification examination, and (2) absence of a uniform and specific training and knowledge base for examiner qualification.

Need for a Medication List

Regarding the topic of a "List," new guidelines for medication use in commercial drivers (which are contained within specific disease guidelines) are continuously being published, but present a "moving target" for examiners' reference. The FMCSA Evidence Reports and Medical Expert Panel Recommendations, as referenced earlier, and a new *Medical Examiners Handbook* (NRCME-FMCSA) are available online. The FMCSA Medical Review Board has also issued new recommendations to the FMCSA regarding medications.

Knowledge Base and Training

Regarding knowledge base and training, the FMCSA Commercial Driver Medical Qualification is evolving rapidly. As this synthesis report was being prepared, the FMCSA announced the Notice of Proposed Rule Making to establish a national registry of medical examiners (FMCSA NPRM Federal Register announcement No. 73FR-73129; Docket No. 2008-0363). The Role Delineation Study performed in support of this initiative identified "Knowledge, skills and abilities" that will guide CDME training and testing content, but did not directly identify the source of these attributes. Because evaluating a driver's use of medication has been associated with at least five essential CDME tasks (see earlier discussion) any training developed would be expected to derive from some common understanding of effects of specific medications on driving ability and performance, independent of the underlying medical condition. Resolving the former issue (List) would likely be needed to complete the latter (training and certification).

Alertness Education for Drivers

Commercial Driver Medical Examiners have not yet been asked to provide drivers with sleep and alertness education, or educational materials, which has already been provided to commercial drivers and their employers through the FMCSA-ATRI-sponsored train-the-trainer courses (O'Neill et al. 1996; Krueger and Brewster 2005). From having discussed this topic with medical examiners in several round table discussions, there appears to be a common opinion among the medical examiners. The medical providers pointed out that it is the driver's responsibility to manage a suitable sleep/wake schedule. Furthermore, they indicated that assigning this fatigue education responsibility to medical examiners would detract from the primary purpose of the examination, and may place the medical examiner in the position of being responsible for driver factors over which he or she has little to no control; they can't "write a prescription for sleep."

Communication with Employers

There are a few generalized findings from the questions asked of the medical examiners about their interactions with the drivers' employers. In brief, some employers seek too much information from the examination process, and many ask for too little.

Employers in one of the two regions surveyed apparently regularly demand the DOT "Long Form" (Form 649-F-6045) from medical examiners performing driver examinations. As a result, in many clinics, before being examined commercial drivers are required to sign an individual release form to permit sharing medical information with their employer. It is unclear what impact this has on the veracity of the answers to the medical examiners' questions of the driver.

Some employers contract with third party administrators to review the commercial driver examinations and to help them ensure compliance with federal rules, providing some oversight for the medical qualification process. A number of other employers permit the drivers to be certified by their primary care physicians, which allows for greater variability in meeting the medical certification standards than either of the two previously mentioned options, but better knowledge of the drivers' underlying health history. This, as the survey respondents indicated, permits a driver to "doctor shop"; to find a doctor who is friendly to the driver's particular needs to remain medically certified.

Some of the synthesis survey respondents indicated (and it has been the personal experience of co-author Leaman) that there has been significant pressure from employers to pass drivers who may not be medically qualified. The request to "do the minimum required" has prompted employers to switch providers of medical services until they identify one who "passes" the drivers, virtually regardless of their medical condition. The medical conditions for which medications described in this report are prescribed have all been at issue.

Medical examiners do not have access to drug testing information performed under 49 CFR Part 40, which frequently identifies opiates or other substances that bear on driver safety and medical qualification. Further, some employers who are contacted by MRO under provisions for "Stand Down" (49 CFR 40.4) become concerned when they are *not* contacted by the medical examiner following an exam where the driver may admit to opiate medication use [permitted with a prescriber's written statement, under 391.41(b)(12)]. This is a particularly acute problem following the discovery that a mishap has taken place.

SUMMARY OF MEDICAL EXAMINER SURVEY

The survey was limited by the small number of participants ($n = 23$) and the selected medication list. A convenience sample survey of a small group of certifying medical examiners in two Western cities was done to illustrate medical examiner decision making and actions regarding medications and alertness education during the course of the examination (CDME). Twenty-three medical examiners were presented with a list of 69 different medications. For each drug, they were asked whether a driver might be medically certified to drive a commercial vehicle while taking the medication and under what conditions, if any. Examiners were also surveyed on what driver education on medication effects, alertness, and employer communications they would normally provide to drivers they examine. Finally, medical examiner handling of the Medical Examination Report "DOT Long Form" (Form 649-F-6045) was described with respect to employer distribution.

The responses within the two groups surveyed, although not statistically representative of all CDMEs, showed that within those groups there was inconsistent decision making that did not always follow FMCSA rules and recommended guidelines. More consistent responses ("I would not issue a certificate") were given with regard to driver use of the drug methadone, which is specifically forbidden, than for other drugs. However, despite the prohibition rule, 3 of the 15 CDMEs answered that they would issue a conditional certification to a driver who admitted using methadone. Overall, of those who indicated they would issue CDME certificates to drivers on an opiate medication or amphetamine, only 6 to 7 out of 23 medical examiners would require a prescribing physician's written statement as required by 391.41(b)(12); only two would require a prescriber note for Tramadol. Drivers admitting to the use of this medication were anticipated to be issued certificates by every provider questioned.

Antihistamines, neuroleptics, sedatives and hypnotics, stimulants, movement disorder medications, heart medications, and assorted other medications were included in the questionnaire, and these produced inconsistent responses by providers regarding actions they anticipated they might take in qualifying or not qualifying drivers who admitted ingesting these classes of medications. Such inconsistencies were found between the two regions surveyed and among providers in both regions.

Only 2 of the 23 examiners indicated that they gave any advice to commercial drivers on maintaining alertness or combating fatigue. Almost one-quarter of the surveyed medical providers admitted they provided "no education" to drivers on effects of medication on alertness. However, when they themselves had prescribed the drug to drivers for medical conditions they were treating, approximately one-half of survey participants anticipated cautioning those drivers about the effects of such medications. No medical examiner surveyed provided drivers' employers with a list of "prohibited" medications.

Employers vary by region about whether they require the DOT Long Form (Form 649-F-6045), with the surveyed group of providers indicating that it was required almost half the time. Medical providers similarly vary by region in terms of the amount of communication they have with employers regarding their specific driver employees. Most of the medical providers who indicated that communication did occur stated in comments that it was either very general on the topic of safety concerns and work fitness or it was on issues the company would likely learn from the MRO under 49 CFR 40.21.

CHAPTER SEVEN

MOTOR CARRIER POLICIES ON DRIVER USE OF CHEMICAL SUBSTANCES

INTRODUCTION AND METHODOLOGY

A structured interview questionnaire for use with CMV stakeholders (e.g., predominately truck carrier fleet managers, safety advocates, and other company officials) was designed to elicit key information about current commercial motor carrier company applications, policies, and programs involving the use, or restriction of use, of chemical substances by commercial drivers. The survey questionnaire asked specific questions about a carrier's knowledge base regarding various chemical substances sometimes ingested by their drivers. It also asked them about current company policies regarding driver use of stimulants, hypnotics, and nutritional supplements. The questions on the survey were open-ended enough to gather information about company officials' experiences with current approaches and procedures, and safety policies in place, to identify problems and to elicit proposed solutions regarding the use of chemical substances in the commercial transportation industries. Survey questions were specifically designed to cover the scope and objectives outlined for the purpose and intent of this synthesis study.

The ATRI distributed the survey questionnaire to motor carrier company officials through: (1) the American Trucking Associations (ATA) Safety and Loss Prevention Management Council; (2) to a health and wellness working group within the council; and (3) to several wellness clinics located at travel centers that target over-the-road drivers. Respondents were solicited by e-mail, accompanied by an Internet URL link on the ATRI's website, where the respondents could access the online version of the Chemical Effects Survey.

QUESTIONNAIRE SURVEY RESULTS

The participants consisted of safety and human resource personnel within the trucking industry, including motor carriers and allied professionals (e.g., motorcoach and health and wellness clinics). Thirty-one company responses were collected. These companies employed a range of from a minimum of 10, to a maximum of 6,200 drivers, with an average of more than 800 drivers (816) per company. Most respondents were representatives of truck carrier firms. The survey netted responses from one commercial driver training company and from one charter-bus company.

The specific questions posed in the survey are depicted in the context of the presentation of the results (here) along with summary statistics for the surveys.

Carrier Survey on Chemical Substance Use among Drivers

1. What sector of the trucking industry do you primarily operate in? (Check all that apply.)

Sector	Total
For-Hire	16
Private	7
Truckload	7
Less-than-Truckload	5
Specialized	2
Other	3

Open-Ended Responses:	Total
Other	
Charter Bus	1
Medical and Wellness Clinics	1
Training	1

2. How many drivers does your company employ (by type)?

Driver Type	Total
Company Drivers	24,490
Leased/Owner–Operators	4,225

3. Do you have company policies or guidance (written or verbal) for drivers on drugs, medications, or other chemical substance use?

Company Policies or Guidance	Total
Yes	29
No	2

If you answered yes to Question 3, please answer Question 4 below. If no, please proceed to Question 5.

4. For which of the following chemical substances does your company provide drivers with policies or guidance? (Check all that apply.)

Type of Policy or Guidance	Total
Prescription Medications	24
Over-the-Counter Medications	12
Legal Stimulants	6
Sleep Aids	8
Nutritional Supplements	3
Alcohol	24
Illegal Drugs	23

Open Ended: Type of Policy or Guidance	Total
Prescription Medications	Advise safety of all prescription meds
	As a CDL driver if this medication could cause a problem with your driving do not use if it causes you to test positive; you could be terminated.
	Prohibited as they cause adverse effects
	Must report any prescribed drug usage
Over-the-Counter (OTC) Medications	Guidance on effects, guidelines for use when off duty first to evaluate effects before performing safety-sensitive functions, fact sheets on common OTC meds provided
	As a CDL driver if this medication could cause a problem with your driving, do not use, if it causes you to test positive you could be terminated.
	Prohibited if they cause adverse affect
Legal Stimulants	Discourage use by providing education on health effects and through wellness fatigue education
Sleep Aids	Awareness communication
	Prohibited if they cause adverse effects
Nutritional Supplements	No responses received
Alcohol	Firm written policy
	Assistance if employee steps forward
Illegal Drugs	Firm written policy
	Zero tolerance if busted, assistance if employee comes forward

5. Do you have an employee Health and Wellness program?

Health and Wellness Program	Total
Yes	19
No	12

6. Does the Health and Wellness program include drivers?

Health and Wellness Program Including Drivers	Total
Yes	19
No	9
No Response	3

If yes, please briefly describe your Health and Wellness efforts here:

Open-Ended Responses
Training materials developed in-house and through Novartis
Just brought the program in with a fund that is awarded by the Chamber of Commerce in our business area. It covers checks for cholesterol, triglycerides, etc. Blood pressure, diabetes. Associated counseling for any problems discovered.
We perform basic awareness. Evaluating options for starting a wellness program.
Company provides guidance regarding good nutrition to employees and ongoing awareness regarding health to the employee.
Health fairs, driver wellness training with practical discussion over the ideas, drivers trained in Drug and Alcohol use.
We provide an onsite workout facility (weight machines, treadmills, free weights). We mail out a monthly health newsletter to drivers' homes.
We are developing a program.
Presentation on exercising and healthy eating. Weight watchers program.
Health care staff comes in once a year to review additional options and to complete minor health care diagnostic work.
Company healthcare.
Our program is just starting, so initially we address diet and smoking.
Primarily promoting healthy life style through messages and handouts. Nondriver employees have sack lunch health meetings.
Roadside Medical (RSM) Driver Wellness Program is designed specifically for the professional driver based on testing from the current state of driver health. RSM is also in the process of creating a line for its employee's monthly wellness program; Introducing the Roadside Medical Driver Wellness Program . . . the most innovative program designed to travel with you! Roadside Medical's Driver Wellness Program provides simple and easy-to-follow tools and materials to get us on the road to better health (and keep us there!). Key features include: unlimited one-on-one telephone health coaching, a wellness kit, a free 30-day health check, exercise and nutrition guides, and more.
New driver 30-day meal supplements kits, designed for the professional truck driver.
Currently they fall under the corporate Wellness Program. We are tailoring this program to be driver-specific, and keeping them under the corporate program.
Annual screenings, preventative testing paid 100% through insurance

7. If chemical substances are included in your Health and Wellness program, please elaborate:

Open-Ended Responses
We offer Employee Assistance Program for all staff
Health coaching
We follow the DOT regulations for hazmat endorsed drivers

8. How are company policies regarding driver substance communicated? (Check all that apply.)

Communication Method	Total
Health and Wellness Program	13
Written Company Policies	31
Safety Meetings and Training	29
Reminders in Employee Newsletters	14
Other Means	2

9. What issues or problems regarding commercial driver chemical use need to be addressed or resolved in our trucking community? (Please identify and elaborate.)

Open-Ended Responses

Education on OTC and prescription medications and their effects.
There needs to a better way to control what drivers are doing once they are out on the road.
As far as being mandatory, there should be no more regulations required of the companies. All illegal drugs, abuse of legal drugs, and alcohol are already covered in our DOT Drug and Alcohol policies.
Sleep
Designer drugs
None we have
Drug database for carriers to reference
Expand to additional drugs and testing processes
Most of our problems with drugs or alcohol are drinking and driving in the driver's personal vehicle (DUI) resulting in loss of CDL.
Need to reduce the number of drivers that need to be randomly tested each year.
Specific guidelines of what is acceptable and what is not.
The drug testing standard needs to move to hair testing.
Providing health/wellness health coaching and counseling. Once you start to help drivers achieve results and their minds become clearer, they need support in recognizing dependencies and how to deal with them LONG-TERM!
Prescription drugs and legal stimulants
Accurate method to determine a driver's alcohol and drug history prior to hiring.
Over-the-counter aids should have warning labels when taken with prescription medications.
Need to make sure all companies are in compliance.
We need a national database showing when and where drivers tested positive. This database should be accessible to all trucking companies so they know a driver's prior history before hiring him or her.

10. Do you have adequate access to chemical substance resources? If yes, what information sources did you find useful?

Adequate Access to Chemical Substance Resources	Total
Yes	22
No	9

Open-Ended Responses

Internet and Internet updates; online information if needed (5 responses)
Seminars sponsored by main health facility we contract with to do our DOT physicals and drug tests.
Employee awareness through J. J. Keller
Through our Medical Review Provider
National Safety Council
Close relationship with our clinics, Employee Assistance Program line
J. J. Keller Health care programs, Employee Assistance Program network
Our Third Party Administrator (TPA) for health insurance, etc.
Coaching and counseling
Consolidated Drug and Alcohol Compliance, Inc., Kenner, LA
We use DOT regulation notices and have a medical staff that keeps our organization informed
Tapes, written programs, and online tools

If no, on what topics would you like more information?

Open-Ended Responses

Information on over-the-counter meds and their effects
Industry best practices
Federal database
Specific information for generic drug names
Easy reference to prescribed and over-the-counter drugs that are restricted or problematic for driver alertness
Providers of testing nationwide

CHAPTER EIGHT

SYNTHESIS CONCLUSIONS AND DISCUSSION

INTRODUCTION

Throughout this synthesis report there are numerous assessment statements, conclusions, discussion, and some identified needs for subsequent research. This chapter is a summary of key points and provides suggestions for logical steps to follow from this work.

FINDINGS FROM THE LITERATURE REVIEW

One of the primary goals of the synthesis was to identify and elaborate on published research regarding the many psychoactive chemical substances that drivers use. In particular, the synthesis team was in quest of information on psychoactive chemical compounds that might play a feasible role in sustaining driver alertness or promoting sleep, and therefore would assist in management of commercial driver fatigue. Although the literature review here does identify several chemical substances that may serve those purposes, this synthesis does not propose, nor prescribe specific usage protocols for any chemical substance described. Rather, it provides a reporting of the highlights of many research studies cited in the scientific literature, with a special focus on identifying those studies that purport to have measured the effects of chemicals on task performance related to roadway driving.

Another goal was to cull through the scientific literature to identify and categorize the reported research on many other psychoactive substances having identifiable effects on the cognitive, psychomotor, and physiological performance of drivers. That is, one of the objectives was to assemble in one source document identification (at least a listing) of what has been published already, so as to ease the task of anyone desiring additional background information on these topics. Thus, in Appendix A, this synthesis presents a description of a variety of chemical substances that drivers partake of, whether the evidence for psychoactive effects was strong or not. Additionally, this synthesis presents in the References, not only a listing of citations used in the narrative text (Appendix D web-only), but also a supplemental bibliographic reading list of secondary source documents that pertain to the topics in this study (Appendix E web-only).

In this synthesis, the coverage of the results of any individual study described within, by necessity, is brief. For more specific details, motivated readers are encouraged to acquire and consult the original journal articles. The literature review here is intended to provide important information to aid in the understanding of:

1. The state of scientific knowledge from published research findings regarding the health and performance effects of numerous chemical substances that sometimes are ingested by commercial drivers;
2. Findings and practices relating to which psychoactive chemicals offer promise to commercial drivers striving to sustain alertness and to manage driver drowsiness or fatigue during partial sleep deprivation, which is so often necessitated by extended freight delivery operations; and
3. What the literature and practice indicate to be acceptable sleep aids for use by commercial drivers in managing their sleep schedules during on-the-road operations, including at times of the day when it is not normally conducive to sleep.

The comprehensive literature review reports numerous laboratory experimental studies of the performance of individuals under the influence of many psychoactive chemical substances. Some of those chemicals (medications, drugs, etc.) have been safely used in various sustained work settings. Predominately, these instances described have been in military operations wherein limited use of varying stimulant and sleep aid compounds has been permitted after a person's experience with the particular compound is established first, voluntary consent for their use is obtained and then only under close medical supervision, with the constant scrutiny and control of safety officers charged to manage operational use of chemicals by their military teammates, partners, or "employees." Most of the experiments and the actual operational use of such chemicals documents examinations of "acute" applications, in which the chemicals or drugs were taken only on a short-term basis, usually lasting no more than several days duration. Only rarely did the reported studies measure drug effects in repeated applications over days and weeks as might be the need for commercial driver applications.

This literature survey therefore reaffirmed that there are only a few viable psychoactive chemical substances that commercial drivers can legitimately and safely use as sleep aids (hypnotics) or as alertness enhancers (stimulants) during transportation operations. The circumstances involved in commercial driving in the United States are somewhat different from those of U.S. military operations. Sanctioned pharmaceutical use in military operations requires controlled

closed-loop medical and safety supervisory settings that stress safe use of psychoactive medications for measured short durations intended to achieve time-limited missions. Such use of medications would likely be very impractical as well as very costly to manage in a commercial driving setting.

Sleep-promoting Compounds

Available sleep-promoting compounds and hypnotics include classes of prescription anxiolytic agents, depressants, anti-insomnia medications, over-the-counter (OTC) sleeping pills, first-generation antihistamines that induce drowsiness, synthetically formulated hormones such as melatonin that promote sleep, and herbal and dietary supplements touted as relaxants. Research studies on each of those categories of sleep-inducers are described in the literature review in this report.

Benzodiazepines

The literature survey confirmed that the variety of benzodiazepines used to induce sleep present a number of serious limitations for operational use in the transportation industry context. As the research results depicted in this survey convey, a large number of the hypnotics described in this report either have already been, or might in the future be, declared unsuitable for commercial driver use on the roadway.

Nonbenzodiazepines

The literature survey also points out that some of the newer prescription sleep-inducing drugs, nonbenzodiazepines with shorter half-lives, may be preferable to older drugs for use as anti-insomnia treatments, because the amount of sleep inertia or hangover effects rapidly dissipate as the drugs clear the body's biological systems. Some of these newer nonbenzodiazepines (e.g., Zolpidem, Zopiclone, Zaleplon, Indiplon, Eszopiclone, Ramelteon, and Alterial) might feasibly be applied to induce short "naps" in sustained work scenarios, and therefore could be evaluated more closely by means of more scientific testing for their potential application as prescribed sleep-inducing compounds in the commercial driving community. Some of these hypnotics are already being prescribed by physicians to drivers, presumably at least to combat persistent insomnia. However, the FMCSA expert medical panel on psychiatric disorders and driver safety recommended "No" to nonbenzodiazepine hypnotics, and stated that a driver must wait seven half-lives if such drugs are used acutely, or seven half-lives plus one week, if under their chronic use (Expert Panel Aug. 2009, p. 7) (http://www.fmcsa.dot.gov/rules-regulations/TOPICS/mep/report/Medical-Expert-Panel-Psychiatric-Psychiatric-MEP-Panel-Opin.pdf).

Melatonin

The popular and natural sleep hormone melatonin, produced synthetically and sold in health food stores, is identified as an available *safe sleep-inducing compound* that can be used without prescription. However, because it is classified as a "health food," the manufacture and distribution of synthetic melatonin is not subject to FDA approval and, therefore, consumers cannot be sure of the quantity, purity, and quality of the product they purchase. More research on "good quality" melatonin could be fostered with a goal of developing recommended operational use protocols (recommended timing, dose levels, duration of use, etc.) for commercial drivers who might benefit from using this more natural sleep promoter. Proper use of synthetic melatonin might be especially beneficial after completing night driving and when daytime sleep opportunities present themselves in over-the-road operations.

Antihistamines as Sleep Aids

It is known that many commercial drivers employ OTC first-generation antihistamines (e.g., those containing diphenhydramine) to obtain relief from seasonal allergies; however, in some applications, drivers take them simply to assist in falling asleep. Several OTC sleeping pills also contain diphenhydramine or similar compounds that induce drowsiness. Appropriate usage protocols (times of administration, dose levels, cautions, and so on) could be developed for use of such sleep-inducing compounds, specifically for application to the many work-rest schedules inherent in the commercial driving community. Additional research may be required to examine the combined use of melatonin and antihistamines as sleep aids.

Additional research could be done to confirm whether or not the newer second- and third-generation antihistamines declared to be nondrowsy, are as efficacious for treatment of seasonal allergies as their advertisements claim. Then, protocols for their appropriate and safe use for treatment of allergies should be developed and promulgated for the commercial driving community.

Alcohol to Induce Sleep

As the literature review confirms, the use of alcohol to put one to sleep brings about risks that the sleep, and of REM dreaming sleep as well so obtained may be disrupted in the later, deeper stages of sleep and therefore may not be as restful as intended. With larger amounts of alcohol there is always the risk of hangover upon awakening.

Stimulants and Alertness Enhancing Compounds

A large number of alertness-enhancing or wake-promoting compounds is available; however, it appears there is no solid scientific foundation for finding most of them suitable for use in commercial driving applications. Whereas caffeine, nicotine, and energy booster supplements are viewed as being acceptable for driving situations, almost all other effective (efficacious) stimulant drugs are not. Some stimulant compounds are illicit and illegal drugs (e.g., cocaine) and are deemed too deleterious to driving performance to permit their

use during operations on the road. For those licit-prescribed Schedule II stimulants, an FMCSA expert panel has opined that there is inadequate evidence for or against their safe use in commercial driving, and recommended "continued monitoring" of the medical literature (Hartenbaum et al. 2006).

Modafinil

Described as an eugregoric compound (and therefore not an amphetamine-like drug), a "wake-promoting substance," modafinil offers much promise for use as a stimulant, with probable application to the commercial driving community. Modafinil has been shown to increase alertness, memory, and planning activities in healthy adults. As laboratory research described in the review indicates, modafinil provides many of the same stimulant benefits that caffeine and other stronger stimulants provide, but with slightly different physiological side effects, some of them less offensive, such as not being as threatening to blood pressure as caffeine. A very important and interesting observation about modafinil is that, unlike any other stimulant (including caffeine), while a person is taking modafinil, he or she can still decide to go to sleep; that is, to take a nap without interference from the "drug." That feature of modafinil could be explored in subsequent research programs.

Although several U.S. military medical laboratories continue to research modafinil, more research could be specifically designed to answer questions regarding the potential wider application of modafinil (or armodafinil) to commercial driving scenarios. In particular, research could help develop a suitable "usage protocol," including identification of recommended dose levels, the time of day of administration, the time of administration within a work shift or during adjustments to shift changes, any limitations for the duration of more long-term usage of modafinil or armodafinil (e.g., weeks/months), and determination of whether or not there are interactions with other chemical compounds drivers consume, especially caffeine and antihistamines. Financial affordability of these relatively expensive medications might also be an inhibitor to commercial driver use.

Caffeine

Caffeine, the ubiquitous stimulant compound, is the most widely consumed psychoactive substance available. The literature demonstrates that caffeine offers a relatively safe and effective means of maintaining or restoring cognitive performance even under conditions of operational stress (see numerous citations in text). Caffeine restores cognitive function during prolonged wakefulness, and it can enhance certain types of cognitive performance, most notably vigilance and reaction times, in rested individuals, regardless of whether or not they are regular caffeine users. The doses of caffeine most likely to be effective without causing undesirable mood effects are within the range of 100 to 600 mg, and this amount of caffeine can easily be obtained in many readily available sources, including by drinking caffeinated coffee.

Even with the significant amounts of caffeine research cited in the literature review however there does not appear to be a conveniently available "recommended caffeine use protocol" for how much (dose) and when to take in caffeine during commercial driving operations. The paucity of actual highway driving studies examining effects of caffeine suggests that more research on this obvious fatigue countermeasure needs to be focused on delineating numerous usage protocol variables for commercial driver alertness and fatigue management programs. It would be helpful to have an information packet that provides basic information about protocols for the use of caffeine, pointing out at least that as with any stimulant, the body adjusts to large intakes of caffeine, necessitating larger doses to obtain the same effect; that it takes about 20 min after consuming caffeine for the stimulation effects to kick-in; and that depending on the time of consumption before attempting to sleep, caffeine will affect sleep latency, quality, and restfulness. The differences in caffeine formulation (e.g., coffee, soft drinks, chewing gum, mints, and energy bars and drinks) also could be delineated and a description of some of the physiological side effects of caffeine use (e.g., raises blood pressure and nervousness) could be provided as well.

One aspect of the research on caffeine that may warrant further exploration is the potential value of combining slow-release caffeine and a short nap (30 min) a technique reported as being successful in counteracting drivers' sleepiness in a partial sleep deprivation study. Not much information was located regarding either slow-release caffeine or combining naps with such stimulants as fatigue countermeasures.

Nicotine

Although nicotine is classified as a stimulant, the scientific literature describing its effects with regard to cognitive performance is equivocal. Whereas some laboratory evidence presented indicates that nicotine can produce the enhancement of certain aspects of attention and cognition, no studies report true enhancement of sensory abilities, selective attention, learning, and other cognitive abilities such as problem solving and reasoning. Furthermore, nicotine has been demonstrated not to be effective in restoring alertness and cognitive performance during laboratory testing of sustained performance in the face of full sleep deprivation (48 h). Accordingly, any informational packets prepared for the commercial driving community should clearly highlight known facts to dispel common myths held about nicotine's positive utility. Too many drivers are under the misimpression that the nicotine in their cigarettes will help maintain their alertness, and research illustrates that it probably does not.

Supplements: Nutritional, Dietary, and Other

A very large number and a wide variety of supplements are available and are being consumed by a large cross section of Americans, no doubt including numerous commercial drivers. As the literature survey herein suggests, the synthesis team

located only a few reports of experimental studies on most of the chemical compounds identified as *supplements* in this document. Although some scientists searching for the "ideal stimulants" quickly discount the variety of supplements widely sold in truck stops and convenience stores, it is clear that commercial drivers are purchasing them. It appears incumbent on this community of researchers involved with commercial drivers to systematically examine the efficacy of many "supplements," and then to recommend protocols for their safe use. Accordingly, any risks associated with using these supplements, alone or in combination, or owing to concerns about their source and their purity, should be identified and the findings promulgated.

Guarana

Guarana (a caffeine-like substance) is showing up in many food and drink supplements, often in combination with other ingredients, some of them also touted as being psychoactive substances (e.g., caffeine, taurine, and ginseng). Guarana's caffeine-like ingredients, and its somewhat similar positive effects on cognitive performance to those of caffeine itself, suggest that guarana, alone or in combination with other substances, should be investigated further. Additional research on guarana is called for to identify its effects individually and synergistically with other psychoactive ingredients in food and drink supplements. Then educational materials could be developed to promulgate the findings in the commercial driver safety community.

Herbal Relaxants

Herbal remedies are promoted to relieve stress, and promote relaxation and sleep. Although a number of herbal relaxants (e.g., passion flower, lavender, kava, valerian, ginseng, and St. John's Wart) are described in the literature review here (see chapter five and Appendix C), not many qualifying scientific studies were found attesting to their efficaciousness, nor their potential effects on performance. A study to identify the increased use of such substances in the commercial driving community could determine whether or not subsequent controlled experiments of them are warranted.

Nutritional Food Supplements

Nutritional food supplements, amino acids, additional carbohydrates, antioxidants, multi-vitamins, and a myriad of others are described briefly in the literature review (see also Appendix C). At first glance, it does not appear that much additional research on these items is warranted, at least not by way of prioritization in comparison with the other supplements that should be investigated further, such as those listed in the previous paragraph. However, because drivers and their employers are inquisitive about what they see, hear, and read about, it is important to describe what is known about some of the more widely advertised nutritional food items and to incorporate that information in some "hand-out" literature on the whole category of supplements outlined in the literature review in this synthesis.

Functional Energy Drinks

The active ingredients (caffeine plus others) in some functional energy drinks (FEDs) were found to impact (interrupt) some aspects of daytime sleep following a simulated night shift. These researchers concluded that whereas FEDs may be effective "pepper-uppers" for a single night shift, additional investigatory research is warranted into the use of FEDs over successive night shifts; and also to investigate the effects of drinking multiple containers of FEDS on the same day—that is, daily dose determinations. The commercial advertising media has barraged the public with countless claims of the benefits of new energy drink products. The daily use of popularly sold energy drinks (e.g., Red Bull™, Monster Hitman™ shots, and a dozen others containing psychoactive substances) is quite widespread. The synthesis team suggests that some good laboratory research on this category of supplements is warranted to set the record straight regarding their efficaciousness, or lack thereof, and, if possible, to delineate any recommended use protocols and identification of risks or hazards in consuming such products.

RESULTS AND DISCUSSION OF MEDICAL EXAMINERS SURVEYS

Since at least the 1970s, the use by commercial drivers of supplements, drugs, and prescribed medications has been recognized as accident-associated features of transportation crashes, without clearly identifying specific casual inference (NTSB studies and reports). Medical providers and examiners are frequently faced with decisions to qualify (or not qualify) drivers who admit to taking medications and prescribed psychoactive chemical substances, many of which are not covered or not covered consistently in published guidance from the FMCSA (Graziano et al. 2011). The convenience survey of medical examiners in this synthesis study gave insights into some aspects of how they conduct their work in accomplishing Certification of Driver Medical Examinations (CDMEs). The survey highlighted some of their knowledge base and the voids, in terms of dealing with chemical substances in their exams of commercial drivers, and it portrayed some differences in practice approach, part of which might be at least regionally based. Although the findings of the survey of 23 medical examiners are outlined in detail in chapter six, some of the more cogent points are reiterated here by way of summary and conclusions.

- *Medical examiner variance.* CDME examiners have varying knowledge, attitudes, and beliefs leading to actions anticipated in certification decisions with respect to drivers who admit to taking prescription,

self-administered medications or drugs, and chemical supplements.
- *Regional differences.* There was significant regional variation in responses (Salt Lake City, Utah, versus Reno, Nevada) that can possibly be attributed to the experience and number of examinations performed by individual examiners.

Medication Survey

Medical Examiner Response Inconsistencies

Surveyed medical examiner responses to particular drugs and medications were inconsistent, and for one medication (Methadone), inconsistent with published federal regulations. For example, in the synthesis survey 8 of 23 surveyed medical examiners indicated they would issue a conditional certificate to a commercial driver who admitted using methadone [forbidden under 391.41(b)(12)]. Tramadol, on the other hand, was acceptable to slightly more than half of the 23 surveyed CDMEs (with detailed history provided in the clinic). Tramadol was an accident associated factor (medication) in at least one NTSB investigated accident (A.J. Barberi, DCA04MM001, Oct. 15, 2003).

Response to Stimulants

Commercial drivers admitting to the use of stimulants provoked mixed and varied responses from medical examiners. More than half of the surveyed examiners (14 of the 23) anticipated providing medical certification to a driver who admitted taking amphetamine. This was most often conditioned on receiving a treating physician's written statement, but could also occur with only a detailed history in clinic (3 of 23). Examiners indicated that medical cards were generally issued for drivers admitting use of prescription stimulants (d-amphetamine, methylphenidate, and modafinil) with or without an accompanying written statement from the prescribing physician and additional medical history in the clinic.

Antidepressants are usually approved for drivers who admit to taking them, after obtaining a detailed history in the clinic—with the exception of lithium (used for bi-polar disorder), for which a provider written statement would be required by more than half of the respondents. Responses from the majority of (but not all) examiners indicated that first-generation antihistamines are frequently (but not always) associated with instructions given to drivers not to take them within 8 h of driving. Second-generation antihistamines had fewer such warnings from the medical examiners.

Neuroleptics and Hypnotics

The broad class of neuroleptic medications queried drew mixed responses. Medications typically used for neuropathy (gabapentin and pregabalin) were conditionally approved for more than three-quarters of respondents, based on detailed medical history or prescribing physician written statements (or both). Drivers admitting use of dilantin, and particularly phenobarbital (typically used to prevent seizures or for neuropathy), were either never qualified or required a prescribing physicians written statements in the majority (but not all) respondents. Sedatives and hypnotics were also generally widely accepted, with the examiners offering advice to the drivers regarding not taking the medication within 8 h or more before driving. Of particular note were the longer-acting sedatives clonazepam and trazodone (an antidepressant frequently used off-label as a hypnotic).

Other Medications

Movement disorder medications appeared on the survey list of medications specifically owing to their use for Restless Legs Syndrome and product warnings for episodes of "sudden onset sleepiness" that have been reported to cause motor vehicle accidents in private vehicles. There appeared to be little awareness of these factors in that only 2 of 23 the examiners surveyed answered "Never issue" and slightly less than half would issue a certificate conditioned on driving no sooner than 8 h for drivers admitting use of pramipexole (Mirapex®) or ropinirole (Requip®). Drivers who admitted use of selected cardiac medications would generally be approved with additional history or a prescriber's written note. Examiners surveyed seldom marked "Never approved." One of the listed medications, dobutamine, is primarily used in ambulatory treatment of severe congestive heart failure. NTSB identified dobutamine as an accident-associated factor in one NTSB investigated crash. [NTSB HAR 01/01 (PB2001-96201)].

Similarly, when asked about anti-arrhythmic amiodarone, only 3 of 23 examiners answered that they would never issue a medical certificate, with the majority indicating that drivers would be required to submit a prescriber's written statement. Other medications with a propensity to cause sedation or adverse drug reactions or interactions, as well as adverse psychological effects, were generally not uniformly handled with respect to certification decisions. This was particularly true regarding varenicline (Chantix®), for which only 35% of surveyed examiners answered they would "Never issue" a medical certification card, despite advisory information to that effect provided by the FMCSA, which had been posted on FMCSA's website in FAQ and in a statement from the administrator.

Driver Education and Employer Interactions

- *Convey little education.* Surveyed medical examiners reported that they generally provided little education or guidance on safe medication use to commercial drivers or their employers in the context of their CDME process.
- *Principal employer communication.* Interactions between medical examiner and drivers' employer, including verbal and making the "Long Form" available to employers were

reported to vary by region, for factors that are unclear from the survey. Medical examiner comments indicated that those who did communicate information about the driver exams to the employers mostly were required to explain only if a driver did not "Pass."
- No lists of prohibited drugs were made available by the medical examiners to employers (motor carriers).

Suggestions for Further Research

The results of the survey of the medical examiners who conduct CDM examinations prompted a number of suggestions for further research:

- To support development of an evidence-based list of approved medications and supplements.
  - The current testing required under Part 40 for illegal drugs of abuse does not fully address accident-associated medication questions for legally prescribed medications or supplements. Research could be undertaken to examine the potential for expanded drug testing of drivers to expand knowledge of actual medications taken (rather than only those admitted) in pre-employment, randomly, and in post-accident settings (similar to rotational testing for drugs of abuse performed by the U.S. military). Expanded post-accident testing for medications, as well as illegal drugs, has been called for in other settings (e.g., Expert Panel on Licit Schedule II drug use).
  - A methodology could be developed to address accident causal inference that would cover the use of medications and other chemical substances (accident risk modeling, similar to fatigue risk modeling).
- To support more consistent practice among medical examiners of commercial drivers with respect to drugs, medications, and fatigue advising:
  - Specific medical examiner training materials could be developed that would focus on medications, separate from the underlying medical conditions, with a view to framing them in the context of previously investigated accidents where the medications have played a role as a causal associated factor.
  - Research could be undertaken toward compiling an anthology of accidents with medications as causal associated factors be published and analyzed from the point of view of the medical examiner. In particular, this treatise should cover those chemical substances identified in commercial driving settings.

MOTOR CARRIER POLICIES REGARDING CHEMICAL SUBSTANCES

With American Transportation Research Institute assistance, 31 company surveys were returned from safety and health officials and other company management personnel. Those that returned surveys (mostly truck carriers) consisted of 16 for-hire, 7 private, 7 truckload, 5 less-than-truckload, and 2 specialized companies. Representing more than 25,000 company drivers, and more than 4,000 leased/owner-operator drivers, the range of the number of drivers was from a minimum of 10 drivers per company to a maximum of more than 6,200 drivers, with an average of 816 drivers per company.

Although 29 of the 31 respondents in the survey indicated that their company had some form of policy regarding driver use of chemical substances, only 24 indicated that they had policies concerning prescription medications, 24 for alcohol, 23 for illegal drugs, and 12 for OTC medications. When asked if they had policies regarding other chemical substances, eight declared they had a policy concerning sleep aids, six for legal stimulants, and three for nutritional supplements.

In answer to the more open-ended questions on the survey, a number of the companies expressed interest in obtaining more usable information, education, and guidance on the many chemical substances available to their drivers (employees). Some companies requested information on what chemical substances are acceptable for use by commercial drivers and which chemicals are not suitable. This in itself suggests that one outcome of this survey done for this synthesis study would be to develop more informative guidance information; "hand out" materials on the most common forms of chemical substances used by commercial drivers.

OVERALL CONCLUSIONS FROM THE SURVEY OF MEDICAL EXAMINERS AND MOTOR CARRIER MANAGERS

- ***Solid information packages are not available.*** All three elements of this synthesis on chemical substances (literature review, and surveys of carriers, employers, and medical examiners) point to the lack of detailed information about the numerous chemicals, drugs, supplements, popular energy enhancement products, and so on that might have an impact on commercial drivers' performance and health. Such information, presented in user-friendly packages, could be of benefit to three communities: (1) commercial drivers and their employers; (2) medical providers who either treat commercial motor vehicle (CMV) drivers or who perform medical certification exams of drivers; and (3) representatives of the commercial driving safety community, researchers, and policy makers, who all must stay abreast of pharmaceutical developments, nutritional supplement marketing, and medical practices that involve the influence of psychoactive chemical substances with CMV driving and roadway safety issues.
- ***Additional research needed on some chemical substances.*** As specified throughout the literature review, and highlighted in the conclusions, transportation researchers concerned with CMV safety issues can identify numerous areas where additional research may be called for regarding the chemical substances available to commercial drivers and that may impact driver performance and health.

APPENDIX A

Additional Research on Chemicals Affecting Performance and Health

This appendix contains descriptive information on a select number of chemical substances, predominately illicit drugs that commercial drivers should not be using in their operations, but for which there is substantial literature describing the effects of such drugs on either human performance or health. In a community wishing to employ and retain only reliable and safe drivers, mandatory compliance, and random urine screening tests of commercial drivers, occasionally detects metabolites of illicit drugs, evidence that some drivers do indeed use marijuana or cocaine as well as other illegal drugs readily available on the street. In using illicit drugs, drivers put their jobs in jeopardy. For the sake of completeness, this appendix contains descriptions of additional chemical substances and describes some known effects on performance, especially cognitive performance.

CENTRAL NERVOUS SYSTEM DEPRESSANTS

Central nervous system (CNS) depressants are often referred to as sedatives and tranquilizers because they are drugs that slow normal brain functions. When taken as prescribed by a physician, depressants may be beneficial for the relief of anxiety, irritability, tension, and as treatment for insomnia. In listing drugs that can be involved with personal abuse, the National Institute of Drug Abuse (NIDA) suggests depressants produce reduced anxiety; a feeling of well-being; lowered inhibitions; slowed pulse and breathing; lowered blood pressure; poor concentration and fatigue; confusion; impaired coordination, memory, and judgment; addiction; respiratory depression and arrest; and, in extreme cases, death. The most common CNS depressants include methaqualone and gamma-hydroxybutyrate (GHB). NIDA reports that depressant drugs of abuse are known by the street names of barbs, reds, and yellows (for barbiturates), as candy and downers (for benzodiazepines), and as ludes and quads (for methaqualone).

Several of the better-known depressants were once commonly prescribed as treatments for anxiety and sleep disorders. In excessive amounts they produce a state of intoxication very similar to that produced by a large intake of alcohol. It is the drowsiness and calmness that depressants cause that brings about the potential for both physical and psychological dependence, and often leads to their abuse.

Impairing effects of depressants typically peak at 2 to 3 h after ingestion, and can last for up to 6 h. After that (or the following morning) there are typically few or no impairments (Ghoneim et al. 1975). However, as long as the sedating effects persist, they may impair driving-related functions and therefore constitute a potential danger in the context of driving (Shinar 2007b). Physiological and physical symptoms of impairment include problems with ocular convergence, increased pulse rate, a decrease in body temperature, horizontal gaze nystagmus, and poor coordination as reflected in the walk-and-turn test. In this respect, the effects of CNS depressants are similar to those of alcohol—the most commonly abused depressant (Schnechtman and Shinar 2005; Shinar 2007a).

In a review of 35 studies of different CNS depressants (barbiturates, nonbarbiturates, tranquilizers, and antidepressants) Clayton (1976) grouped the effects into sensory and perceptual, cognitive, and motor functions. Clayton reported that most of the depressant drugs did not produce significant impairments on most of the laboratory tasks measured. However, of the sensory and perceptual functions, critical flicker fusion and dynamic visual acuity were impaired by several of the drugs, whereas static acuity, depth perception, and visual search were relatively immune to the drugs tested. Of the cognitive skills, there was slight evidence of impairments on short-term memory tasks, although mental arithmetic was relatively unaffected. Of the commonly tested motor tasks, the one most significantly impaired was tracking. Shinar (2007b) reported that for every finding of a significant drug effect cited in Clayton's review there were at least four others where the impairing effects were not statistically significant. Clayton (1976) explained why it is so difficult to reach firm conclusions about practical effects of prescribed psychotropic drugs on driving performance by citing differences in methodology, tasks used in testing, drug doses, and in choice of test participants. Since Clayton's 1976 review, experimental studies of drug effects and other literature reviews have not substantially clarified the picture (Shinar 2007b). This synthesis briefly reviews some descriptive literature on specific CNS depressants.

The first three CNS depressants described, methaqualone, GHB, and flunitrazepam, are of little direct interest in the context of this synthesis, which is directed at commercial driving concerns, but are briefly described here for the sake of completeness in addressing the drugs listed in the NIDA chart of illicit drugs that could be used as hypnotics (chapter three).

Methaqualone

Methaqualone, a synthetic sedative, is normally administered orally, and is rapidly absorbed from the digestive tract. Intoxication effects include euphoria/depression, poor reflexes, slurred speech, and, with large doses, possibly coma. Continued use in large doses can lead to tolerance and dependence. In the 1970s and 1980s, methaqualone was sold under various

brand names such as Quaalude, Sopor, Parest, Mequin, Optimil, and Somnafac. NIDA lists additional street names for methaqualone as ludes, mandrex, quad, and quay. When it was more popular, methaqualone was widely abused on the street, and it caused many cases of serious poisoning. No literature is cited here for methaqualone as it is an inappropriate drug for the commercial driving community.

Gamma-hydroxybutyrate

Historically, gamma-hydroxybutyric acid, gamma-hydroxybutyrate (GHB) has been used in a medical setting as a general anesthetic to treat conditions such as insomnia, clinical depression, narcolepsy, and, more rarely, alcoholism, and to improve athletic performance (Benzer 2007). NIDA lists GHB effects as causing drowsiness, meaning it could be listed as a hypnotic. GHB is approved by the FDA (as Xyrem™) for medical use in treating cataplexy and excessive daytime sleepiness in patients with narcolepsy, a condition incompatible with the profession of commercial driving.

GHB administered as a liquid may act directly as a neurotransmitter, but is unusual because it crosses the blood–brain barrier after oral administration. GHB is also a metabolite of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA); thus, it is found naturally in the brain, but at concentrations much lower than doses that are abused (NIDA). The exact mechanism of action of GHB is unclear; however, some evidence suggests it may modulate dopamine activity, specifically by increasing the availability of cerebral dopamine. GHB's effects on the CNS include sedation and, in higher doses, even coma. Some research reports on a paradoxical mix of sedative and stimulatory properties of GHB, as well as a so-called "rebound effect," experienced by individuals using GHB as a sleeping agent, wherein they awake suddenly after several hours of GHB-induced deep sleep (Mamelak 1989). GHB also has been investigated as an anesthetic agent, and when used this way has few effects on cardiovascular or respiratory systems (Buysse et al. 2005).

NIDA lists street names for GHB as G, Georgia home boy, grievous bodily harm, and liquid ecstasy. GHB has significant abuse potential. It is classified as one of several "club drugs" used to facilitate date rape, particularly when combined with alcohol (see the NIDA website on club drugs: www.nida.nih.gov/infofacts/clubdrugs.html). GHB is an illegal drug in many countries. Adverse health consequences associated with GHB include nausea/vomiting, headache, loss of consciousness, loss of reflexes, seizures, coma, and possibly death. No literature is cited here on GHB, as it is not of practical pertinence to the commercial driving community.

Flunitrazepam

Flunitrazepam is a CNS depressant frequently associated with sexual assault (date rape). NIDA lists the various street names: Rohypnol: forget-me pill, Mexican Valium, R2, Roche, roofies, roofinol, rope, rophies. One effect is memory loss for the time a person is under the drug's effects. Side effects include visual and gastrointestinal disturbances, and urinary retention. No studies regarding health or performance with flunitrazepam are cited here, as it is not an appropriate drug for the commercial driving community.

BARBITURATES

The barbiturates Amytal, Nembutal, Seconal, and Phenobarbital were once among the drugs most frequently prescribed by physicians to induce sedation and sleep. Barbiturates are identified as ultrashort, short, intermediate, and long-acting depending on the time it takes for the effects to occur after the drug has been taken. Small doses calm nervous conditions, and larger doses cause sleep 20 to 60 min after being taken orally. Intoxication effects of barbiturates include sedation, drowsiness and depression, unusual excitement, fever, irritability, poor judgment, slurred speech, dizziness, and life-threatening withdrawal (NIDA 2006). As with other depressants, if the dosage of a barbiturate is increased, the effects may progress through successive stages of sedation to sleep, coma, and to death (Davis 1996). Because of the significant risk of barbiturate addiction, approximately 15 years ago physicians began prescribing other drugs to induce sedation and sleep. NIDA lists street names for such barbiturates as barbs, reds, red birds, phennies, tooies, yellows, and yellow jackets.

Two studies (Pickworth et al. 1997 and Mintzer et al. 1997) evaluated effects of Phenobarbital on performance, without interactions of alcohol. Results suggested that barbiturates affected psychomotor functions in ways similar to that of alcohol and benzodiazepines. Owing to their dramatic effects barbiturates are no longer considered to be helpful medications to induce sleep in practical workplace applications. Barbiturates may be viewed to a small extent in drivers who are prescribed or take medications for headache syndromes containing butalbital (Fiorinal® or Fioricette®).

Methylphenidate and Pemoline

Methylphenidate (MPH: Ritalin®, Cocerta, Metadate, or Methylin) is a psychostimulant drug belonging to the piperidine class of compounds. It increases the levels of dopamine and norepinephrine in the brain through reuptake inhibition of the monoamine transporters. MPH possesses structural similarities to amphetamine, and although MPH is less potent, its pharmacological effects are even more closely related to those of cocaine, but without all the addictive tendencies. MPH is approved for treatment of attention-deficit hyperactivity disorder (ADHD), postural orthostatic tachycardia syndrome, and narcolepsy; and for off-label use in treatment-resistant cases of lethargy, depression, neural insult, obesity, and obsessive-compulsive disorder. In 1961, the FDA approved the MPH medication as Ritalin® for use by children with behavior

problems, especially ADHD. Methylphenidate is fairly short acting, with the effects lasting approximately 4 h, with a half-life of 3 h (Nishino and Mignot 2005).

Historically, methylphenidate has been used extensively to treat excessive daytime sleepiness associated with narcolepsy and ADHD (Connors and Taylor 1980; Mitler et al. 1986). Most of the research on effects of methylphenidate on performance has been directed toward assisting people who have been diagnosed with ADHD, especially children (see for example Coons et al. 1981; Peloquin and Klorman 1986; Fitzpatrick et al. 1998; DeGrandpre 1999; Fone and Nutt 2005); but also for the treatment of narcolepsy (e.g., Mitler et al. 1986).

Other studies demonstrated some positive effects of MPH on information processing in that MPH increased response speed on cognitive performance tasks, but with some accompanying side-effects (Naylor et al. 1985). When these experimenters manipulated response complexity, the drug effect increased as response complexity increased, but was not affected by stimulus complexity. Their data were interpreted to mean that MPH affects response selection rather than stimulus processing. Several other studies reported improvement in accuracy and response speed with administration of methylphenidate in tasks designed to test short-term memory scan (Talland 1970; Coons et al. 1981; Peloquin and Klorman 1986; Brumaghim et al. 1987).

During the late 1980s and early 1990s, U.S. military medical research labs experimented with using either or both stimulants, methylphenidate and pemoline, as potential alternatives to amphetamines in helping to sustain soldier performance during sleep deprived operations (e.g., Babkoff et al. 1992). Babkoff et al. administered 10 mg of MPH every 6 h for eight doses in a study involving 48 h without sleep. About one-fourth of the significant differences between MPH and placebo involved instances when MPH subjects performed worse than placebo subjects. These researchers subsequently abandoned further examination of methylphenidate. One other study, by Bishop et al. (1997), reported that sleepiness, as measured by Multiple Sleep Latency Testing (MSLT), was reduced by 10 mg of methylphenidate given twice per day after one night of sleep deprivation, and performance on reaction time and vigilance tasks was improved. For a meta-analysis comparison of methylphenidate and modafinil, both used as cognitive enhancers, see Repantis et al. (2010).

Pemoline (formerly marketed as Cylert), another CNS stimulant, is structurally different from the amphetamines and methylphenidate, but possesses pharmacological activity similar to other stimulants. Unlike amphetamine, pemoline does not modulate noradrenaline and is reported to be free of adverse effects on mood and the cardiovascular system. In the United States, pemoline was a Schedule IV controlled drug under the Controlled Substances Act. Formerly, pemoline was used to treat ADHD and narcolepsy (Mitler et al. 1986). However, after it was found to have too many complications, such as hepatic failure (liver damage), the FDA withdrew approval in 2005. Pemoline was effectively withdrawn from the pharmaceutical marketplace in both Canada (1999) and the United States (2005). However, 4-methylaminorex, a more potent analogue of pemoline, has recently appeared as a black market drug with abuse potential similar to methamphetamine (Rodriguez and Alfred 2009).

Although in the research programs (e.g., at the U.S. Naval Health Research Center) positive effects with both MPH and pemoline were somewhat equivocal, pemoline demonstrated a better chance of countering the effects of sleep loss. Even though initially pemoline demonstrated the potential to reverse sleep deprivation effects (e.g., Gelfand et al. 1968; Babkoff et al. 1992; Nicholson and Turner 1998) it never really gained much favor relative to other available stimulants (e.g., modafinil). Studies of both MPH and pemoline quickly were displaced with laboratory examinations of other stimulants to meet the military's needs.

No reports examining either MPH or pemoline and driving performance per se were located. As was mentioned earlier, pemoline is now virtually gone. Although drug tests for MPH are not normally performed with drivers, MPH has been identified in post-mortem studies of highway traffic crashes, but generally not so in aviation crashes.

ANTIDEPRESSANTS

Robbe and O'Hanlon (1995) administered a dose of 77 mg/day of the tricyclic anti-depressant amitriptyline and found it produced severe drowsiness and strikingly impaired performance on nearly every test on the first day, but its effects were practically gone after 1 week of treatment. Amitriptyline is frequently used off-label as a hypnotic for sleep induction and/or maintenance at lower doses. Another antidepressant, paroxetine, a Selective Serotonin Reuptake Inhibitor, administered in the usual dose of 20 mg, had no effect on performance. Paroxetine at 40 mg did not affect road tracking but slightly impaired performance in some psychomotor tests in a persistent manner (Robbe and O'Hanlon 1995). Ramaekers et al. (1994) reported that when mianserin (10 mg 3xd) and doxepin (25 mg 3xd) were administered for 8 days, mianserin and doxepin both impaired driving on day 1; however, after 8 days of doxepin treatment impairments dissipated, but not during mianserin treatment. O'Hanlon and Freeman (1995) stated depression itself and the chronic use of the antidepressant amitriptyline are associated with a greater than normal risk of traffic accidents. Otherwise, impairments associated with depression generally resolve in those patients showing a favorable response to antidepressant therapy, regardless of the drug. These findings must be individualized however owing to the varying responses to therapy.

In April 2010, the FAA announced a new policy on antidepressants. On a case-by-case basis, pilots who take one of four antidepressant medications—fluoxetine (Prozac), sertra-

line (Zoloft), citalopram (Celexa), or excitalopram (Lexapro) will be allowed to fly if they have been satisfactorily treated on the medication for at least 12 months.

COCAINE

In addition to the stimulants described in chapter four, there is an extensive literature about the performance effects of a few others; notably cocaine. Cocaine acts on the CNS by stimulating the cerebral cortex, and it mediates psychostimulant effects by blocking catecholamine reuptake (mainly dopamine). Cocaine's structure is different from amphetamine-like compounds (Nishino and Mignot 2005). It is most often used as a part of a vasoconstricting topical anesthetic. Cocaine, often abused outside of a medical setting, generally gives rise to a sense of well-being, which is dose-dependent (Rush et al. 1999). Increased alertness and motor performance are often reported by cocaine users (Epstein et al. 1999). The duration of effect is usually between 30 and 90 min. The usual dose would be an oral, nasal, or injection dose ranging from 50 to 300 mg. Injection or inhaling no more than 1 to 1.5 mg/kg (maximum dose 50 mg) just prior to activity produces the effects within minutes. A cocaine-like amphetamine (96 mg) did not improve performance in research subjects before sleep loss; however, cocaine significantly improved reaction time performance and alertness as measured by the Profile of Mood States rating scale after 24 and 48 h of sleep loss (Fischman and Schuster 1980).

In a series of studies, researchers at the Southern California Research Institute (SCRI) examined cocaine effects on driving performance. Twenty-four healthy males, ages 21 to 40 years, who were self-admitted cocaine users, participated. An initial experiment with cocaine (96 mg intranasaly) and alcohol (0.58 g/kg) found no impairment of driving-related laboratory tasks attributable to the cocaine (Moskowitz and Burns 1989). In a second experiment, with 96 mg of cocaine, subjects performed better with cocaine than with placebo, with the greatest differences observed during a test battery beginning 3 h after dosing. Because the second test time coincided with the anticipated afternoon physiological lull, the findings raised questions about the drug effects and circadian rhythm (Burns 1993). Burns reported further studies of time-of-day differences associated with cocaine's effects. In a nighttime experiment, divided-attention and vigilance data agreed with the previously reported afternoon data. When subjects were tested near midnight, scores were better with cocaine than with placebo, and the effects of cocaine on performance persisted past the period of acute stimulation. Divided-attention reaction times were faster with 96 mg of cocaine, whereas 126 mg of cocaine prevented slowing of vigilance response times. Burns concluded that cocaine effects may be task-dependent, as well as dose-dependent (Burns 1993).

Chronic use of cocaine leads to drug addiction and related problems. The use of large amounts of cocaine can cause tachycardia, hypertension and ventricular fibrillation, hallucinations, nausea, vomiting, anorexia, convulsions, coma, and death. A single dose of 1.2 g of cocaine could be fatal; however, death is also known to have occurred with a dose as small as 20 mg. Hyperthermia, resulting from peripheral vasoconstriction, is a potentially serious problem with continued cocaine use and therefore cocaine can be potentially lethal for those doing exercise (or work) in very warm environments or hot climates. Interestingly, cocaine and adrenaline enhance the other's sympathomimetic effect.

Nonmedically supervised cocaine use is illegal in the United States. The risks of using cocaine, especially a high likelihood of drug addiction, far outweigh any perceived ergogenic benefits. Use by commercial drivers or other heavy equipment operators can result in job loss. For these reasons, no additional research on cocaine is reported here.

CANNABINOIDS [THC FROM MARIJUANA AND HASHISH]

Cannabinoids are compounds extracted from the cannabis sativa plant (marijuana) or the cannabis indica plant (hashish—Arabic word meaning grass), or they can be produced synthetically. They also can be produced in the body after ingestion and metabolism of cannabis, or even occur naturally within the body or brain (Solowij 1998; Shinar 2007b). Marijuana or THC dependency can develop with chronic use. In the United States, in states where it is permitted, chronic treatment with *medical marijuana* is legitimately prescribed as a sedative because it is used for treatment of some medical conditions to reduce sensation of chronic pain and discomfort. Legitimate medical uses for THC include treatment of pain, anorexia, and chronic illness such as AIDS or cancer. Under Federal Regulations Part 40, medical marijuana is not authorized for commercial driver's license (CDL) holders.

Marijuana is normally considered to be a recreational drug in the form of dried tops and leaves of the cannabis sativa plant. NIDA lists street names for marijuana as blunt, dope, ganja, grass, herb, weed, joints, Mary Jane, pot, reefer, sinsemilla, and skunk; and for hashish, names such as boom, chronic, gangster, hash, hash oil, and hemp. The primary psychoactive cannabinoid found in both marijuana and hashish is delta-9-tetrahydrocannabinol (THC).

Because of the time it takes to reach the blood stream, the effects of THC are quicker and greater when it is smoked (e.g., in marijuana cigarettes), with time-to-peak levels in the brain being about 7 to 8 min. If it is inhaled into the lungs, marijuana effects are noticeable almost immediately. When marijuana is taken orally (eaten), the psychoactive peak effects appear within 10 to 30 min, and may remain for about one hour, but dissipate after more than 1 to 2 h. The half-life of THC is about one week; however, THC gets absorbed into body fat, and traces of THC metabolites (such as THC–COOH) that by themselves have no psychoactive properties can be detected in urine for as long as a month following ingestion (Chesher 1995).

Unlike alcohol, THC does not distribute evenly in all tissues, and its rate of absorption and elimination is different for experienced and inexperienced users. The method of measurement of THC in the body greatly affects the implications for impairment and the estimated time of ingestion. Although the subjective level of a psychological or a physiological "high" experienced by participants in well-controlled marijuana studies is highly correlated with the THC level in the blood stream (Robbe 1994), it is difficult to assess and determine a relationship between a person's THC blood or plasma concentration and performance impairing effects.

Physiologically, THC raises a person's heart rate and has CNS effects. Cannabinoid receptors are concentrated in several distinct regions of the brain (the cerebellum, hippocampus, basal ganglia, and cortex) and therefore the effects of THC are quite varied. Although THC does not have a large effect on sensory functions, it impairs cortex-mediated higher-order perceptual functions, resulting in distorted time and distance perception (Laberge and Ward 2004; NHTSA 2005; NIDA 2006).

The most commonly noted psychological effects of marijuana and the THC contained therein include enhanced mood, in which individuals normally feel better; but effects might also include irritability and disturbance of memory and judgment (Croft et al. 2001). It impairs cognitive functions that result in slowed thinking and reaction time, impaired memory and learning, difficulties in sustaining or shifting attention, and in problem solving. Marijuana also impairs motor functions leading to loss of coordination and to impaired balance (NHTSA 2005), and marijuana users may experience sensations of confusion, anxiety, euphoria, and sleepiness (Shinar and Schechtman 2005; Shinar 2007b). These performance degradations manifest themselves in driving (Smiley 1999). However, in experimental situations, subjects can often "pull themselves together" to concentrate on simple tasks for brief periods of time, thus making it difficult to generalize from lab findings of performance effects to real life scenarios (NHTSA 2003, 2005; NIDA 2005).

A series of lab-based studies in the Netherlands (Robbe and O'Hanlon 1993; Robbe 1994) examined effects of marijuana on actual driving performance. After subjects smoked standardized marijuana cigarettes, they drove in traffic for 64 km (~40 miles) at speeds of up to 100 km/h (~62 mph). A commonly employed lab-based standardized test [standard deviation of lateral position (SDLP)] measured driving impairment in the form of vehicular weaving. Plasma specimens were analyzed for THC and its carboxy metabolite (THC-COOH). It was concluded that: "THC's effects on SDLP were equivalent to those associated with BACs [blood alcohol concentrations] in the range of 0.3–0.7 mg/mL. Other driving performance measures were not significantly affected by THC. THC's effects after smoking doses up to 300 mg/kg of hashish never exceeded those of alcohol at BACs of 0.8 mg/mL." Robbe and O'Hanlon (1993) said "it appears not possible to conclude anything about a driver's impairment on the basis of his/her plasma concentration of THC and THC-COOH determined in a single sample."

In the marijuana research program sponsored by NHTSA, but conducted in the Netherlands, the conclusions in the NHTSA final report read in part:

> This program of research has shown that marijuana, when taken alone, produces a moderate degree of driving impairment which is related to the consumed THC dose. The impairment manifests itself mainly in the ability to maintain a steady lateral position on the road, but its magnitude is not exceptional in comparison with changes produced by many medicinal drugs and alcohol. Drivers under the influence of marijuana retain insight in their performance and will compensate, where they can, for example by slowing down or increasing effort. As a consequence, THC's adverse effects on driving performance appear relatively small. [*Source*: NHTSA final report, Nov. 1993 (DOT HS 808 078)].

Carter (1980) studied effects of chronic marijuana use in Costa Rica. Subjects were 86 chronic marijuana users and 156 nonusers. The users self-reported smoking an average of 10 marijuana cigarettes a day for a minimum of 10 years and an average of 17 years. The cigarettes contained 1.3% to 3.7% THC. Some of the marijuana user subjects earned their living by driving trucks, buses, or taxies, and some preferred to drive while under the influence of the drug. The study discerned no real consequences of prolonged use of the drug as it reported: "no hard data were obtained regarding the effect of marijuana use on driving ability" (Carter 1980). McBay reported that Carter's findings were in keeping with controlled studies carried out in Jamaica and Greece. Although Beirness et al. (2005) reported the incidence of cannabis in motor vehicle crashes, until actual driving studies are performed that report blood concentrations in heavy chronic marijuana users, one can only speculate what the long-term effects might be (McBay 1997).

A NIDA study examined the performance effects of several drug classes using repeated measures design. Eight volunteers were administered two doses of ethanol (0.3 and 1.0 g/kg), marijuana (1.3% and 3.9% THC), amphetamine (10 and 30 mg), hydromorphone (1 and 3 mg), pentobarbital (150 and 450 mg), or placebo on separate days (Pickworth et al. 1997). The larger dose of each drug increased subjective reports of drug strength; however, only ethanol and pentobarbital impaired performance on circular lights, digit symbol substitution, and serial math tasks. Both ethanol and pentobarbital impaired performance on card-sorting tasks, wherein impairment was evident at lower doses as the cognitive load increased. Results illustrated differences among drugs producing performance impairment at doses that cause subjective effects. Increasing cognitive requirements (increased workload) detected performance impairment at lower doses. Marijuana had a significant effect on a serial add–subtract task in that response time was significantly slower (46%) by the 3.9% THC marijuana cigarette smokers at 30 min. Marijuana did not have a significant effect

on the other 13 performance measures in the study. Pickworth et al. (1997) stated that their results differed from those of several studies that showed performance impairment after smoking marijuana.

In a meta-analysis by Berghaus et al. (1998) of 60 studies that examined cannabis results, as well as 197 studies of alcohol effects, both the similarity of THC and alcohol-related impairments and their differences were illustrated. They are similar in that at some level of drug dose both affect a wide variety of cognitive functions. They are dissimilar in that the level of blood alcohol needed to show impairment is nearly the same in all studies, with the median approximately 0.07% (slightly above the threshold for driving in most European countries and slightly below the threshold for automobile drivers in the United States); by contrast, the range of THC concentrations needed to affect the various cognitive functions is quite large, with some functions—the inter-related functions of tracking, psychomotor behavior, and driving/simulator performance—being impaired at low THC levels, whereas others—such as information processing and visual functions—are impaired at much higher THC levels (Heishman et al. 1990, 1997; Wilson et al. 1994; Ramaekers et al. 2004). Shinar says this is important because the uniformity of impairment with alcohol provides a rationale for setting specific BAC limits, whereas the lack of uniformity for THC concentrations makes it difficult to determine safe driving threshold levels for THC.

Berghaus et al. (1998) conducted an extensive review of 87 findings on the effects of THC dosing on various driving-related psychomotor tasks. They reported that the dose-response relationship is not very consistent, and surmised that when inhaled the effect of cannabis peaks within the first hour, and diminishes afterwards. However, when eaten (digested), the effects may be delayed 1 to 2 h. Even under careful experimental conditions, within the first hour of smoking and with a high dose of more than 18 mg/ml THC, 40% of study results failed to demonstrate THC impaired performance. The tests reflected a mix of psychomotor tasks, some very sensitive to THC, and some not. The most sensitive tasks, the ones that show the greatest and most consistent impairments, are the ones that involve attention, tracking, reaction time, learning, and short-term memory. Recall of information learned after cannabis ingestion is greatly impaired, whereas recall of information in long-term memory is not impaired (Ramaekers et al. 2004).

Even though crash statistics suggest alcohol is involved in a far greater number of highway crashes, cannabis intoxication is still very much a problem (perhaps in some countries more than others) in that significant numbers of highway crashes, many of them fatal, are at least in part attributable to driving under the influence of marijuana. Laumon et al. (2005) examined fatal crash incidents in France for 10,748 drivers with known drug and alcohol concentrations involved in fatal crashes (2001 to 2003); they reported 681 drivers tested positive for cannabis, including 285 with an illegal BAC (>0.5 g/l). The presence of cannabis was associated with increased risk of responsibility (odds ratio 3.32), and a significant dose effect was identified. The prevalence of cannabis (2.9%) estimated for the driving population is similar to that for alcohol (2.7%). At least 2.5% of fatal crashes were estimated as being attributable to cannabis, compared with at least 28.6% for alcohol. Although alcohol may be the bigger problem in France, the study concluded that driving under the influence of cannabis increases the risk of involvement in a crash (Laumon et al. 2005). Ojaniemi et al.'s (2008) assessment of crash statistics in Finland illustrated that cannabinoids may be an even more pronounced problem in more than 27% of that country's highway crashes, and Jones (2005) and Holmgren et al. (2007) indicated positive findings of THC in 20% to 25% of crashes in Sweden. Baldock (2007) reported similar concerns over the influence of marijuana in injury crashes in Australia, as did Kelly et al. (2004) and Longo et al. (2000a, b). Some of these seemingly high crash numbers no doubt are in part attributable to the more lax approach to use of marijuana and highway safety enforcement rules in several European countries.

In summary, cannabis impairments to performance (1) are not very consistent; they dissipate quickly after about an hour so that just a few hours after ingestion they are no longer significant, even though cannabinoid metabolites can be detected in the urine for several weeks after ingestion; (2) are recognized as troublesome in traffic safety regulations enforced in some countries (including the United States), but not others (e.g., Costa Rica); and (3) raise additional concerns over whether or not regular users become addicted to marijuana and other illegal substances.

The incidence of numbers of commercial drivers in the United States who participate in marijuana or hashish use is largely unknown. However, it is generally believed that because of enforced random urine screening for this and other illegal drugs, and the impending threat of losing one's job and livelihood, the rate of users in the transportation industry seems at least manageable from a safety standpoint [this observation is largely based on the personal experiences of the first author, G. Krueger, during a decade of teaching and interacting with more than 4,000 safety and risk managers in alertness, fatigue, and health and wellness courses (Krueger and Brewster 2002, 2005)].

EPHEDRINE (MA-HUANG)

Ephedra is a plant containing the stimulant ephedrine, an over-the-counter substance found in dietary supplements and weight loss products (e.g., Xenadrine™, Ripped Fuel™, and other commercial names). Along with its alkaloids, ephedrine takes on street names as Desert Herb, Joint Fir, Popotillo, Sea Grape, Yellow Horse, and Teamster's Tea. Ephedrine is a known stimulant that produces sympathomimetic actions, which act on alpha and beta adrenergic receptors in the CNS

and periphery. It is also a dopaminergic agonist (Angrist et al. 1997). Ephedrine fuels metabolism, causing irregularities in thermoregulation; that is, the body produces more heat. Ephedrine alkaloids increase cardiac output and muscle contraction, raise blood sugar, and serve as a bronchodilator to open bronchial pathways for easier breathing (Astrup et al. 1991). In the past, ephedrine was used as a CNS stimulant in narcolepsy and depressive states (Nutto 1983). More recently, ephedrine has been replaced by alternative treatments for these disorders.

The usual dose is 24 mg orally. The duration of ephedrine effects is from 6 to 8 h (plasma half-life 3 to 6 h), with drug clearance from the body within 24 h (Angrist et al. 1997). It is claimed that ephedrine makes a person more alert, gives an energy lift, suppresses appetite, and is commonly used in attempts to lose weight. Many athletes have taken ephedrine for various purposes in their work-out routines, especially for weight control. It is claimed that ephedrine enhances aerobic and anaerobic capacity, muscular strength, and muscular endurance. Ephedrine has been demonstrated to have thermogenic properties, and it promotes fat metabolism (Vallerand et al. 1989) particularly when taken in combination with caffeine.

Ephedrine has been shown to reduce the perception of physical fatigue (Moolenaar et al. 1999). However, there is a paucity of data to support declaring ephedrine to be an ergogenic aid or for actually having long-term weight loss value.

Preliminary research on cognitive functions finds that ephedrine enhances vigilance; but there is insufficient published information to confirm that. Although no reports examining ephedrine and driving were located, Moolenaar and colleagues (1999) examined the effects of 60 mg of ephedrine on a 3-way divided attention task (which they called a driving-related task) for an uninterrupted 4-h period, during which numerous physiological measures were monitored for 15 participants. The performance of a placebo group deteriorated over time, whereas the performance of the ephedrine group improved. They concluded the development of fatigue was partially offset by a single therapeutic dose of ephedrine. No real conclusions can be made about ephedrine and driving-like performance on such scant data reports; more research on that aspect of ephedrine would be required.

There are known hazards with ephedrine use (Bell et al. 1999). Pittler et al. (2005) reviewed the literature for adverse events of herbal food supplements taken for body weight reduction. For herbal ephedra and ephedrine-containing food supplements, they found reports of increased risk of psychiatric, autonomic or gastrointestinal adverse events, and heart palpitations. Therapeutic doses of ephedrine can cause minor hand tremors, increased blood pressure, tachycardia, fear, anxiety, restlessness, and insomnia. Long-term use is not recommended. Severe side effects include high blood pressure, rapid heart rate, dizziness, seizures, strokes, heart attacks, even death. Overdoses can cause paranoid psychosis, delusions, cerebral hemorrhage, and cardiac arrest.

For a decade or more (circa 1990s–2005), following the lead of the weight-room athletes, many Americans took ephedrine as an ingredient in numerous over-the-counter *diet pills* in attempts to control their body weight. Then new fears about adverse side effects attributable to ephedrine came to public light. There have been newsworthy reports of prominent athletes taking ephedrine and experiencing heat stroke, followed by cardiac arrest, leading to multiple organ failure and even death on the playing field. These incidents pointed out the real risks associated with ephedrine, especially when exercising in the heat. Those reports of serious adverse events with ephedrine prompted the FDA to prohibit its sale in dietary supplements; however, it is still available in various forms in select locations in the United States (Schweitzer 2005).

Anecdotal reports periodically surface indicating that some commercial drivers take ephedrine in some form, at least occasionally. Some commercial drivers who have problems with weight control (numerous truck drivers are known to be obese) take ephedrine as a component of commercially available dietary compounds in their attempts to control their weight. For some drivers who fancy themselves as being athletic, there still may be a misguided belief that ephedrine will help them keep physically fit and also alert. However, because ephedrine produces too many untoward side effects and adverse reactions it is recommended that commercial drivers steer clear of ephedrine. Getting the word out to drivers to avoid ephedrine has not been completely systematic.

Caffeine Combined with Ephedrine

The technique of combining caffeine and ephedrine has been used in several forms of diet pills in the United States. The advertising claims benefits include improved vigilance, enhancements in mood, reduced fatigue, quicker reaction times, and improved accuracy at mental arithmetic (Baranski et al. 2001; TTCP 2001). As for the mode of action, both substances (ephedrine and caffeine) stimulate the CNS. Ephedrine is also an agonist for peripheral α and β adrenergic receptors. Caffeine is an antagonist of CNS and peripheral adenosine receptors, also thought to modulate release of Ca++ from sarcoplasmic reticulum. Together they may potentiate each other, and physical performance is enhanced (Astrup et al. 1991; Young et al. 1998; Pasternak et al. 1999). The duration of the combined effect of caffeine and ephedrine is about 5 to 8 h, with peak plasma concentrations occurring 1.5 to 2 h after ingestion. Clearance of one drug is normally not affected by clearance of the other (Bordeleau et al. 1999).

Studies by Bell and colleagues examined the effects of combinations of caffeine and ephedrine on running performance and found that the combination raised metabolic heat production and posed risks of hyperthermia during exercise-

heat stress (Bell and Jacobs 1999). In a study of 2 h of brisk treadmill walking in a 40°C hot, dry environment, Bell and colleagues (1999) observed that increased metabolic heat production was offset by increased heat dissipation and the internal body temperature change was not greater than during a control trial. They also found caffeine combined with ephedrine produced improvements in vigilance, performance of mental arithmetic in terms of both speed and accuracy, and reaction time. Mood was also enhanced, and fatigue state was lessened (Bell et al. 2001).

Haller and Benowitz (2000) reported the likelihood of adverse cardiovascular and CNS events resulting from use of ephedra-containing supplements, which makes the use of a caffeine-ephedra combination inadvisable. Although hyperthermia is more likely when prolonged, strenuous exercise and intense environmental stress are concurrent, the effects of caffeine in this situation have not been adequately examined (Institute of Medicine–Committee on Military Nutrition Research 2001).

There is insufficient information to make a definitive judgment on the combined effects of caffeine and ephedrine on cognitive performance. More research on this topic to determine those combined effects would be warranted if it were not for the known adverse effects of ephedrine reported earlier, which makes the entire issue moot.

In terms of the hazards associated with taking combinations of the two stimulants; nausea and vomiting has been reported in lab and field studies when hard exercise is performed after ingesting combinations of caffeine and ephedrine. Other potential side effects include insomnia, nervousness, anxiety and wakefulness, minor hand tremors, increased blood pressure, and appetite suppression; all such symptoms dissipate within 24 h of cessation of use.

As is mentioned in the section on ephedrine, during the past decade there have been high visibility (newsworthy) events involving the untimely deaths of prominent professional and collegiate athletes whose deaths were attributed to the use of commercially available ephedrine while exercising in high heat and high humidity. These tragic cases each witnessed dramatic effects on body temperature regulation during humid, heat-stress-producing conditions. Subsequent public warnings to all athletic teams have advised against the use of ephedrine. The conditions of the use of ephedrine by the general public, perhaps in the form of dietary pills that likely also contain caffeine, and any propensity to consume such pills along with additional amounts of caffeine (perhaps simply by drinking coffee) is unknown. Recently, the sale of ephedrine in dietary supplements has been prohibited by the FDA (Schweitzer 2005). Despite the ban, many ephedra products are still sold on the Internet. Their purchase and use should be avoided.

APPENDIX B

U.S. Military Policies Regarding Use of Hypnotics and Stimulants

INTRODUCTION

In January 2009, a team of six prominent members of the Aerospace Medical Association (AsMA) published a position paper regarding the use of fatigue countermeasures in aviation. The position paper (Caldwell et al. 2009) espouses numerous operator fatigue mitigation strategies and countermeasures highlighting the need for sleep management, work-rest scheduling, copious use of nap-taking, and so on. Because of the implications of that position paper for all transportation modes, it is of particular importance in this synthesis to reference their comprehensive coverage of research and recommendations concerning the use of pharmacological agents (both hypnotics and stimulants) as countermeasures to sleep-deprivation, fatigue, and associated problems in aviation operations (both military and civilian aviation situations are addressed). Their work also has implications for the commercial driving community (truck and bus/motorcoach operators). The treatise here is largely extracted from that position paper (Caldwell et al. 2009).

> Although differences exist between civil and military operations, it is clear similar factors and conditions lead to fatigue in both civilian and military aviation environments and fatigue mitigation strategies for both contexts should be scientifically based. Understandably however, different regulations and operational considerations have resulted in fatigue countermeasure approaches that differ in important ways. For example, a variety of pharmacological countermeasures have been approved for use in certain circumstances by U.S. military aviators but not by civilian aviators. The current prohibition regarding use of pharmacological countermeasures by civilian pilots can be attributed to safety concerns and issues of adequate policies for oversight. The military services have addressed these issues through targeted research, explicit policies on medical oversight, and recognition of the sometimes overriding importance of operational considerations (e.g., US NAVMED P-6410 2000).
>
> The use of pharmacological countermeasures to fatigue in civilian (but not military) pilots is addressed by Caldwell et al. (2009).

HYPNOTICS AND AVIATION

For circumstances where sleep is difficult to obtain in operational contexts, pharmaceutical strategies (espoused by Caldwell et al. 2009) include U.S. Air Force and U.S. Army approval of limited use of temazepam, zolpidem, and zaleplon. [Only the U.S. Army continues to authorize limited use of triazolam (Halcion®) for pre-deployment rest or sustained operations—although in actuality it is rarely prescribed]. These three hypnotics Caldwell et al. (2009) state can optimize the quality of crew rest in circumstances where sleep is possible, but difficult to obtain. The choice of which compound is best for each circumstance they say must take several factors into account, including time of day, half-life of the compound, length of the sleep period, and the probability of an earlier-then-expected awakening, which may increase the risk of sleep inertia effects. Table B1 lists the categories of hypnotics and their conditions of use as outlined by Caldwell et al. (2009). Each of the U.S. military services has its own policy concerning the use of hypnotics. Table B2 summarizes the U.S. military policies for hypnotic use (predominately specified for military aviation operations). Just as is followed with the military use of stimulants, a ground test with hypnotics under controlled conditions is necessary prior to use during operations. The U.S. Navy guidance explicitly forbids administration of more than one dose of a hypnotic per 24-h period, with no more than two doses of consecutive use of temazepam. There is also guidance for planning and briefing in the grounding restriction (U.S. Navy OPNAV Instruction 3710.7S 2001). As with other medications, the use of hypnotics is voluntary. The reader is referred to the review of military pharmacological policies by Caldwell et al. (2009) for details on the specific "treatment protocols" for use of temazepam, zolpidem, and zaleplon in military aviation settings.

Caldwell et al. (2009) also look toward the potential military aviation application of some of the newer hypnotics available to help with sleep maintenance because they offer a shorter half-life than the extended longer half-life of temazepam. For example, the extended-release zolpidem (Ambien-CR®) improves sleep maintenance beyond that of zolpidem (Greenblatt et al. 2005). Eszopiclone (Lunesta®) has a half-life of 5 to 6 h with minimal residual drug effects after as little as 10 h post-dose (Leese et al. 2002). Ramelteon (Rozerem®) is a novel hypnotic in that it targets the melatonin receptors in the brain in order to regulate the body's sleep–wake cycle, and research indicates this drug is efficacious for sleep onset, but not for sleep maintenance (Lieberman 2007). Caldwell et al. also mention the new hypnotic indiplon, which should be on the market in the near future. Indiplon is similar in structure to zaleplon and has a half-life of approximately 1.5 h and is being formulated with a modified release that will extend its half-life to aid in sleep maintenance (Ebert et al. 2006). There also are new compounds that are rapidly absorbed and that have a short half-life, and several have the ability to increase both slow-wave sleep and slow-wave activity, which improves sleep efficiency. These compounds may improve sleep efficiency to the point that effective wakefulness can be sustained on fewer than the 8 h of daily sleep now required (Caldwell et al. 2009). These developments should be carefully watched to determine their potential applicability to the commercial driving community.

As for current civilian aviation policy, the FAA only allows limited use of zolpidem (Ambien®) and at that no more

TABLE B1
LIST OF HYPNOTICS AND THEIR USES

Generic Name	Brand Name	Dosage	Average Half-Life	Recommended Use	Cautions
Temazepam	Restoril® Euhypnos® Normison® Remestox® Norkotral®	15–30 mg	9 h	Sleep maintenance; daytime sleep	Need 8 h sleep period; not recommended if on-call
Zolpidem	Ambien® Stilnox® Myslee®	5–10 mg	2.5 h	Sleep initiation; intermediate-length naps; assisting early sleep onset due to early bedtimes from shift or time zone change	
Zaleplon	Sonata® Starnoc®	5–10 mg	1 h	Sleep initiation; short naps; assisting early sleep onset due to early bedtimes from shift or time zone change	Not recommended if on-call

Source: *Aviation, Space and Environmental Medicine* (Caldwell et al. 2009).

than twice per week, stating it cannot be used for circadian adjustment. In addition, there is a 24-h grounding policy for any pilot who uses zolpidem. Caldwell et al. (2009) suggest that the FAA's policy that hypnotics not be used for circadian disruption is overly restrictive because it is precisely for this reason that hypnotics would be useful for pilots crossing multiple time zones or flying early morning flights. They suggest that rather than permitting a choice of only one hypnotic, if they allowed a choice of a variety of hypnotics with varying length of action that policy would encourage selection of the appropriate drug for the specific time of use. These authors offer recommendations for permitting use of additional hypnotics in civilian aviation. Interested readers are referred to Caldwell et al. 2009 for details.

Caldwell et al. (2009) suggest that sleep-promoting compounds can be useful in operational contexts where there are problems with sleep initiation or sleep maintenance.

TABLE B2
U.S. MILITARY POLICIES FOR USE OF HYPNOTICS

Medication	Dose	Half-Life	Grounding
U.S. Army Rest Agent Policy			
Temazepam (Restoril®)	15 or 30 mg	8.0–12.0 h	24 h
Triazolam (Halcion®)	0.125 or 0.25 mg	2.0–4.0 h	9 h
Zolpidem (Ambien®)	5 or 10 mg	2.0–2.5 h	8 h
Zaleplon (Sonata®)	5 or 10 mg	1.0 h	8 h
U.S. Air Force No-Go Pill Policy			
Temazepam (Restoril®)	15 or 30 mg	8.0–12.0 h	12 h
Triazolam (Halcion®)	Not authorized	N/A	N/A
Zolpidem (Ambien®)	10 mg	2.0–2.5 h	6 h
Zaleplon (Sonata®)	10 mg	1.0 h	4 h
U.S. Navy Sleep Initiator Policy			
Temazepam (Restoril®)	15 mg	8.0–12.0 h	7 h
Triazolam (Halcion®)	Not authorized	N/A	N/A
Zolpidem (Ambien®)	5 or 10 mg	2.0–2.5 h	6 h
Zaleplon (Sonata®)	Not authorized	N/A	N/A

Source: *Aviation, Space and Environmental Medicine* (Caldwell et al. 2009).
N/A = not available.

However, they state that as with all medications there are both benefits and risks associated with the use of hypnotic compounds. The risks should be considered by the prescribing physician (flight surgeon) and the individual pilot before the decision to use hypnotic therapy is finalized. If the crewmember is likely to be called back to duty earlier than anticipated, then a hypnotic of any type probably should not be used because this would put the pilot at risk of performing flight duties before the medication has been fully metabolized.

Although temazepam, zolpidem, and zaleplon are widely recognized as being both safe and effective, operational personnel should be cautioned about potential side effects and instructed to bring these to the attention of their physician should they occur (Caldwell et al. 2009). For reasons related to anticipated side effects, military personnel are required to receive a test dose of the hypnotic of interest under medical supervision before using the medication during actual operational situations. Further, even after the test dose yields favorable results and it is clear that operationally important side effects are absent, hypnotics should be used with particular caution when the aim is to aid in advancing or delaying circadian rhythms in response to time zone shifts. Reviews by Nicholson (1990), Stone and Turner (1997), and Waterhouse et al. (1997) offer detailed information on this rather complex issue (Caldwell et al. 2009).

STIMULANTS DURING MILITARY OPERATIONS

There is a sizeable literature base describing U.S. military research, mostly by medical research laboratories, on the application of a select number of stimulant drugs by military personnel, to demonstrate possible protocols for usage during training or actual military operations. In particular, work with aviators has examined dextroamphetamine stimulants (e.g., predominately dexedrine) with helicopter pilots (e.g., Caldwell et al. 1995, 1997, 2000a, b; Caldwell and Caldwell 1997, 2000a, b), with fighter jet pilots (e.g., in simulators by Caldwell et al. 2004), and in actual combat operations reported by Schultz and Miller (2004a, b) and Gore et al. (2010), in bomber aircraft operations (Kenagy et al. 2004); and exemplified in the United Kingdom's Royal Air Force use of pemoline in air operations (e.g., Nicholson and Turner 1998). It is beyond the scope of this synthesis to detail the numerous studies and their findings here.

The same team of AsMA scientists mentioned earlier regarding hypnotics also detailed research that informed U.S. military policies regarding the use of stimulants in military aviation (Caldwell et al. 2009). These authors stated that one option for sustaining wakefulness of flight crews during extended missions wherein adequate crew rest is not feasible is to employ alertness-enhancing medications (stimulants). Caldwell et al. (2009) prefaced their treatise by stating that these compounds should not be considered a replacement for adequate crew rest planning and they should never be considered a substitute for restorative sleep. However, they state that in sustained aviation operations the occasional use of the alertness-enhancing medications such as dextroamphetamine (authorized by all three U.S. military services) and modafinil (authorized for use in the U.S. Air Force) can often significantly enhance the safety and effectiveness of sleep-deprived personnel.

Modafinil (ProVigil®)

Particular research studies on modafinil were described in this synthesis in chapter four. Caldwell et al. (2009) suggested that modafinil is gaining popularity as a way to enhance the alertness of sleepy personnel, largely because it is considered safer and less addictive than compounds such as the amphetamines. Modafinil also produces less cardiovascular stimulation than amphetamine and, despite its half-life of approximately 12 to 15 h (Robertson and Hillriegel 2003), the drug's impact on sleep architecture is minimal. Caldwell et al. (2009) reminded readers that modafinil has not been as thoroughly tested as dextroamphetamine in real-world operational environments and some data suggest modafinil is less effective than amphetamine (Mitler and Aldrich 2000). Caldwell et al. (2009) indicated that the U.S. Air Force has approved the use of modafinil in certain long-range combat aviation missions, and it is likely the U.S. Army and the U.S. Navy soon will approve of use of modafinil as well.

Amphetamine (Dexedrine®, Dextrostat®)

Dextroamphetamine (5 to 10 mg) has been authorized for use by all three U.S. military services for certain types of lengthy flight missions (i.e., 12 or more hours of flight). Some of the research described in chapter four supported policy decisions concerning use of amphetamines in the three U.S. military services (for details, see Caldwell et al. 2009). Caldwell et al. (2009) recommend the use of dextroamphetamine in doses of 10 to 20 mg (not to exceed 60 mg per day) for situations in which heavily fatigued military pilots simply must complete the mission despite dangerous levels of sleep deprivation. The following stimulant use protocol guidance, which Caldwell et al. (2009) attributed to the U.S. Air Force, is extracted from their report.

U.S. Air Force Combat Aviation Operations Guidance for Use of Stimulants

- Prior to the operational use of dextroamphetamine or modafinil, an informed consent agreement must be obtained to ensure that crews are fully aware of both the positive and the potential negative effects of these compounds.
- The decision to authorize the use of alertness-enhancing compounds should be made by the Wing Commander in conjunction with the Senior Flight Surgeon.
- All distribution of alertness-enhancing medications must be closely monitored and documented.
- Ground testing (during non-flight periods) is required prior to operational use.

- The currently authorized dose of dextroamphetamine is 5 to 10 mg, and although the dosing interval is not explicitly stated, a 4-hour interval is often recommended. No more than 60 mg should be administered in any 24-hr period, and often, no more than 30 mg are administered.
- The currently authorized dose of modafinil is 200 mg every 8 hours, not to exceed 400 mg in any 24-hour period; however, recent F-117 research has indicated that 100 mg doses also are efficacious (and this lower dose is authorized as well).
- The use of alertness-enhancing compounds normally can be authorized in fighter missions longer than 8 hours or bomber missions longer than 12 hours (although exceptions can be made).
- Caffeine generally is not considered to be a suitable alternative for modafinil or dextroamphetamine; however, caffeine in the form of foods or beverages may be consumed without restriction. Caffeine in the form of tablets or capsules can only be used after flight surgeon approval.

Source: Aviation, Space and Environmental Medicine (Caldwell et al. 2009).

U.S. Army and U.S. Navy guidance is mostly consistent with that of the U.S. Air Force (listed earlier), with the most notable exception being that modafinil is not currently authorized in the Army or Navy. The U.S. Army guidance for use of dextroamphetamine endorses the administration of 5- or 10-mg doses and specifies that no more than 30 mg may be used in any 24-h period. The medication is not be used to sustain wakefulness for longer than 64 continuous hours. U.S. Navy guidance suggests dextroamphetamine be administered in 5-mg doses, which may be repeated every 2 to 3 h; however, total dosage should not exceed 30 mg in any 24-h period. The Navy does not specify an upper level for the duration of any period of continuous wakefulness, but it is clear that extended periods without sleep should be avoided (Caldwell et al. 2009). After citing many research reports related to the topic, Caldwell et al. recommended that all three services sanction the use of modafinil under guidance consistent with that currently followed by the U.S. Air Force (and described earlier).

Caffeine use is a relatively uncontrolled stimulant in the three U.S. military services, and Caldwell et al. (2009) recommended that aircrews should avoid habituation to caffeine and take advantage of its cortical stimulant properties when it is needed to help ensure safe operations. More specifically, when aircrews are not suffering from the effects of fatigue, they should limit their total daily caffeine consumption from all sources to 200 to 250 mg of caffeine per day. Additional doses of caffeine should be used during situations in which fatigue elevates the risk of a mishap. In any 24-h period the total amount of caffeine consumed should not exceed 1000 mg. Aircrew members are to be reminded of the 4 to 6 h half-life of circulating caffeine and preplan its use such that post-duty day sleep is not disturbed by the caffeine consumed.

With the exception of caffeine and various nutritional supplements, no alertness-enhancing medications are currently authorized for use in any type of civil aviation operation. Caldwell et al. (2009) suggested that because civil aviation operations generally are more predictable than military operations, and since prolonged periods of sleep deprivation are not the norm in civil operations (but are almost unavoidable in the military), meaning in civil aviation that other allowances can be planned on, it would seem prudent to withhold widespread authorization of prescription alertness enhancers in the civilian aviation sector.

Intense military operations are generally time limited, in that they expose military pilots to only relatively brief periods in which intense sleep deprivation necessitates administration of appropriate counter-fatigue medications (Caldwell et al. 2009). Because the continuous combat conditions in Iraq and Afghanistan have now been extended over several years, many military pilots have been exposed to pharmaceutical intervention on what comes closer to chronic rather than acute circumstances. A concern in civil aviation operations has always been that if such medications were authorized, commercial pilots might continue day-in and day-out for weeks, months, years, and even for the duration of a pilot's career, which in effect could potentially expose moderately fatigued pilots to years of chronic medication use. Caldwell et al. (2009) take the position that this difference between military and civil aviation operations argues against widespread authorization of alertness-enhancing drugs in civil operations.

ASSESSMENT OF MILITARY USE OF HYPNOTICS AND STIMULANTS TO SUSTAIN ALERTNESS

To the MaineWay synthesis team it would appear that the cautions mentioned previously for treating differences in military versus commercial and civil aviation operations hold equally true, if not more so, for the commercial driving and transport industries. Much of what takes place in operational employment of chemical countermeasures in select military applications does not readily transfer one-for-one to potential utilization of pharmaceutical countermeasures in commercial driving settings. This is particularly true when one considers that the military's policies include ensuring *tight controls over the use of psychoactive substances* in training and during military operations. This just would not be feasible or practical in commercial driving scenarios.

However, there are elements of the military medical research findings that can benefit the commercial driving community, such as the possibility of use of stimulating compounds such as modafinil and caffeinated chewing gum. Under current hours of service rules, which require daily ten-hour off-duty rest periods and include such facets as 34-h weekly restart rest periods, the military protocols used with ultra-short hypnotics to induce sleep might make some sense in selected applications in the commercial driving industries. Continuing new developments in military medical research and applications should be carefully monitored for their potential applications for safe transportation operations.

APPENDIX C

Nutritional Supplements for Inducing Relaxation, Tension Release, Sleep, and More

HERBALS FOR RELAXATION AND STRESS ALLEVIATION

Herbal product caution. As with other nutritional supplements not subject to FDA rules, commercial herbal products may also be adulterated with unlabeled ingredients (Miller et al. 2000; Straus 2002; IOM reports 2005, 2008). Consumer care must be taken to ensure that any potential adverse interactions between some herbs and prescription medications are identified and considered during medical treatment. This is especially important before undergoing medical surgeries wherein the interaction of herbal effects and varying forms of anesthesia may cause serious bodily complications (Izzo and Ernst 2001). Patients planning to undergo surgery are strongly advised to convey what herbs and other supplements they may be taking to the surgeon and anesthesiologist well before surgery and to be sure to discuss the implications.

Passion Flower

Passion flower is an herbal medicine product used medicinally for stress-alleviating purposes. It consists of an extract of raw material taken from an herbal plant (passiflora incarnate or passifloraceae) with street names of maypop or apricot vine. Passiflora, a perennial vine that may reach 10 m in length, was discovered by Spanish explorers in Peru in the sixteenth century. The ten-petal flower was seen as being symbolic of the passion of Christ (which gives it its catchy name), as it was considered as a sign of divine approval of the Spanish conquest. Various species of the passiflora plant are native to North America and are found in the Midwest and Southeastern United States, and as far south as South America.

The medicinal parts of the passiflora plant include the whole or cut dried herb and the fresh aerial parts. For centuries, passion flower has been used as a calming and relaxing herb and as a folk remedy to treat anxiety. Passion flower herb contains free flavonoids (e.g., apigenin, luteolin, quercetin, and campherol), sterols, chlorogenic acid, volatile oil, and traces of alkaloids (harman, harmine harmaline, and harmalol) (Gruenwald et al.'s *PDR for Herbal Medicines* 1998; Kamaldeep et al. 2004). Passiflora has complex action on the central nervous system (CNS). The pharmacologic activity of passion flower likely derives from the flavonoids and alkaloids. A few studies document sedative action of passion flower in humans. Among the claims for passion flower are that it relieves tension; reduces restlessness, anxiety, and nervousness; and that it induces sleep (Kamaldeep et al. 2001). Proponents recommend it for use by people who wish to feel relaxed in the evening after a stressful day.

In 1978, the FDA prohibited use of passion flower in over-the-counter products because it had not been proven to be safe and effective (Robbers and Tyler 2000). However, passion flower is still available as an herbal remedy and is available as a bulk herb in teas, capsules, and as fluid or tincture or in the form of hydroalcoholic extracts. It has been found to exhibit different effects between the alcohol extract and the aqueous extract. The alcohol extracts proved to be anxiolytic and the aqueous extract more a sedative in experiments with mice (Soulimani et al. 1997). Passion flower is sold as a commercial product for both oral and topical administration. It can be used as a tea, usually 2 to 4 grams of the dried herb taken two times per day. In well-advertised U.S. commercial sales of the herbal passion flower, its extract is frequently mixed with other relaxant herbs such as valerian and skullcap. It is incorporated as a principal component of a natural herbal product called Good Night Rx™, which, as with most herbal supplements, also contains numerous other ingredients, including kava.

Assessment of Passion Flower. No reports were located describing studies of passion flower's effects on actual induced sleep quantity or quality, or on resultant effects on human performance. Recommendations are to monitor any new developments that may evolve in the supplements market.

Kava Kava

Kava Kava (piper methysticum) is a somewhat bitter drink containing psychoactive kava pyrones, deriving from the massive gnarly rootstock of the kava-kava shrub. Kava Kava is an integral part of life in the Polynesian South Pacific Islands, as it normally serves as a pleasant drink at the end of a workday. In Fiji, Samoa, and Tonga, the Kava root is dried before it is processed into a powder for use in the Kava drink (Kilham 1996; Lemont et al. 1997). Kava has been prescribed as an effective folk remedy for anxiety, insomnia, and back pain. Its history of use largely as a celebratory drink dates back 3,000 years. In the West, Kava is used much the same way alcohol is used at weddings, public festivals, and on holidays, and in ceremonies honoring the dead. Unlike alcohol, kava does not produce or stimulate aggression, and it does not produce hangover.

In the 1990s, U.S. nutritional supplement companies introduced products that touted kava's anti-anxiety properties (e.g., Pacific Sensuals produced an elixir called "Erotikava"). Kava products are available in liquid or powdered extract form. Taken in sufficient quantities, kava is said to produce a mild natural "high." As a natural herbal drink, Kava-Kava is said to have subtle psychoactive properties, and it is claimed to help relax muscles, calm nerves, and to create a general feeling of well-being, peace, relaxation and contentment, and

to enhance mental alertness and concentration. The ritual of "kava time" involving kava preparation and drinking affords a social time and an opportunity for individual meditation. Claims are that drinking kava produces delightful, pleasurable, relaxing, happy, and peaceful experiences with complete mental alertness (Lebot et al. 1992). South Pacific Islanders have found other medicinal uses for kava, including to help ease anxiety and depression, and to produce restful sleep. Kava is used by athletes as well as businessmen to help "take the edge off" and to focus concentration. Kilham (1996) reported that kava is a first rate sedative, producing a state of calm, and promoting sleep if taken in sufficient quantity. The German Commission E (approximately equivalent of the U.S. FDA) approves kava for treating conditions of nervous anxiety, stress, and restlessness.

Because kava tends to reduce appetite, after drinking it near dinner time people usually consume smaller amounts of food. When taken in moderate doses, kava does not produce identifiable side effects. The compounds called kava-lactones and pyrones are primarily what gives kava its kick, and may result in numbing of the mouth, providing mild pain relief, and muscular relaxation. The most significant anti-anxiety studies show that an effective daily dose of kava is 70 to 210 mg of kava-lactones, or 60 to 100 mg of kava-pyrones daily. Kava has not been shown to be physically addictive, but overuse can lead to health problems such as shortness of breath, dry scaly skin, and slight alterations in red and white blood cells and platelets. Taking kava with alcohol, barbiturates, or psychoactive drugs will produce a multiplier effect. Driving automobiles or operating heavy machinery should be avoided when combining kava with other such psychoactive substances.

In addition to its psychoactive attributes, an interesting side effect of kava is that there have been reports the extract of the kava root depletes the body of vitamin A and, under chronic use, that kava adversely affects night vision—a key requirement for commercial drivers who spend a considerable amount of time driving at night (Russo 2007).

Assessment of Kava. An insufficient amount of quality information about kava was located to make definitive statements about it here. Kava is a chemical substance readily available in the supplement marketplace (particularly in Hawaii) and its place within the commercial drivers' collection of likely substances being consumed should be investigated.

Valerian

Valerian preparations include extracts derived from the roots of the plants genus *Valeriana.* Most of the more than 400 extracts available in the United States and Europe are derived from the species *Valeriana officinalis.* These extracts contain a number of chemicals with CNS activity, including sesquiterpenes, valepotriates, valerianic acid, and other alkaloids. Commercial valerian preparations include a combination of these chemicals in unstated proportions (Houghton 1999). Buysse et al. (2005) stated that given the multiple chemicals that constitute therapeutic extracts it is not surprising the pharmacokinetics and mechanism of action of valerian preparations have not been well described.

Valerian is used to induce sleep. Doses used in clinical studies typically range from 400 to 900 mg per day. The effects of valerian extracts on sleep in humans have been investigated in healthy young adults, and with middle-aged and older adults with insomnia. Subjective effects of valerian preparations included decreased sleep latency, improved sleep quality, and decreased awakenings (Leathwood et al. 1982; Lindahl and Landwall 1989). Effects on polysomnograph measures of sleep include increased stage 3 and 4 and reduced stage 1 nonrapid eye movement (NREM) sleep (Schulz et al. 1994; Donath et al. 2000). Buysse et al. (2005) reported that although improved sleep latency and sleep efficiency have been observed in some polysomnograph studies, sleep continuity effects of valerian are inconsistent (Balderer and Borbely 1985; Schulz et al. 1994; Donath et al. 2000; Taibi et al. 2007).

Side effects associated with valerian have been reported to be few and mild, and include headache, weakness, and some drowsiness, whereas some reports suggest that mixing valerian with alcohol can seriously impair the ability to communicate. Morning sleepiness is an infrequent side effect (Houghton 1999; Buysse et al. 2005).

Assessment of Valerian. No research reports on valerian and performance measurement were located for this synthesis literature review. Monitoring is advised.

Ginseng

Ginseng (American ginseng is *panax quinquefolium*) is a popular nutritional herb, used as an adaptogen and a restorative agent, and thought to relieve symptoms of stress, illness, and fatigue. It has been used to treat nervous disorders, anemia, wakefulness, chronic fatigue, and a host of other maladies. Ginseng is composed of a variety of different substances, including flavonoids, vitamins, enzymes, and minerals. It comes from the root of the *Panaz ginseng* plant, a member of the Araliacae plant family, which grows mainly in China, Korea, and Siberia; but is also available in the United States and Canada. As the ginseng root resembles a tiny man, its name comes from the Chinese words meaning "man-root." There are 11 species of ginseng plants (*Panax genus*); all are slow-growing plants with fleshy roots, available year-round, and all their byproducts are used the same way.

A myriad of different ginseng supplements are available, including in tablets, capsules, powders, teas, energy drinks, nutrition bars, extracts, and as dried roots. The potency of each may vary. It is difficult to compare doses, because the specific ginsenosides to which beneficial effects have been attributed are unknown; moreover, the ginsenoside concentrations vary from product to product (Cui et al. 1994). Ginseng is often

taken orally as a powder (400 to 1200 mg/day) or as an extract (200 to 600 mg/day), and may be taken over a period of from 60 to 120 days. No toxic effects are found with doses up to 4 g/kg for 100 days.

Ginseng has been used medicinally in the Far East, predominately in China, for more than 3,000 years as both an aphrodisiac and an adaptogen, helping people adapt better physically and mentally to the surrounding environment. Ginsenosides are the active ingredient that may produce a corticosteroid-like action, and may indirectly augment adrenal steroid genesis. Ginseng stimulates the CNS. It may alter carbohydrate levels and fat metabolism, and it likely enhances the immune system and promotes an analgesic effect. Ginseng is currently one of the most widely taken herbal products throughout the world. As a general tonic it has been identified with a plethora of physiological effects that combat generalized weakness, fight fatigue, and offer restorative effects for convalescence. However, little empirical evidence is cited to support such effects, and the numerous studies reported are unlikely to stand up to standard scientific methodological scrutiny (Volger et al. 1999).

It is claimed that ginseng enhances the natural resistance and recuperative power of the body and produces both stimulant and sedative activity (Lieberman 2001). Claimed benefits of ginseng taken orally include improved mental alertness, memory, cognitive functioning, and intellectual performance. Mood state also can be positively affected. These effects appear to occur only after chronic use. However, there is a lack of adequately controlled research showing behavioral effects following chronic administration of ginseng in humans (Kennedy and Scholey 2003). Recent research demonstrated that single doses of ginseng most notably engender cognitive benefits in terms of improved memory, but can also be associated with "costs" in terms of attention task deficits following less mnemonically beneficial doses.

As was described under the section on guarana, Kennedy et al. (2004) studied the effects of administering 200 mg of panax ginseng, and a combination of ginseng with 75 mg of guarana. Their experiment with healthy young volunteers determined that both ginseng and the combination of ginseng along with guarana increased the speed of attention task performance and enhanced the speed of memory task performance, with little evidence of modulating accuracy as guarana by itself did. To an extent less than was true with the guarana, ginseng also led to significant improvements in serial subtraction task performance (Scholey and Kennedy 2002; Kennedy et al. 2004). Reporting results of three such studies, Scholey and Kennedy (2002) indicated there was a highly significant and sustained increase in the number of serial seven responses following a 320 mg combination of ginkgo-ginseng at all post-treatment times. This was accompanied by improved accuracy following a 640 mg and 960 mg dose of the combination as well (Scholey and Kennedy 2002). For research examining the combination of ginseng with glucose, and the impact of these two on blood glucose levels and cognitive performance, see Reay et al. (2006).

Recently, ginseng became known as a sports-enhancing supplement for use in enhancing physical performance, with claims that it gives people renewed energy, vim, and vigor (Ziemba et al. 1999). Ginseng has become one of the most popular herbal supplements around for athletically minded people who want to train better and longer. It is estimated more than six million people in the United States take ginseng regularly as a dietary sports supplement. However, thus far, research does not support its claimed benefits. Engels et al. (2003) gave ginseng dietary supplements to 38 young, habitually active adults for 8 weeks, and then asked them to perform a series of all-out effort exercise tests on a stationary cycle. In examining salivary changes in immune response and incidence of upper respiratory infection they concluded that the use of ginseng does not serve well as an ergogenic aid to combat physical fatigue during repetitive strenuous physical exertion. Thus, there is not sufficient evidence to attribute positive effects of ginseng on athletic performance; nor apparently does ginseng enhance psychological well-being (Engels et al. 1996; Cardinal and Engels 2001).

Ginseng has a relatively good safety record. Despite this, it can cause nervousness and excitability in some people for the first few days of taking it, and it may increase blood pressure.

Assessment of Ginseng. Not many experiments were located to relate ginseng to cognitive performance. As suggested by Kennedy and Scholey (2003), further rigorous research on ginseng is needed to delineate its acute effects and to explore the relationship between acute effects and those seen during and following chronic administration regimens.

St. John's Wort

Hypericum Perforatum (St. John's Wort) is purported to have antidepressant-like actions in patients, and to elevate mood and energy in normal individuals. There is no solid evidence of enhanced mental or physical performance, but there is modest indication of mild antidepressant-like activity in human studies.

As with most medicinal herbs St. John's Wort may contain a number of biologically active compounds, including hyperforin. Field et al. (2000) reported that St. John's Wort has catecholaminergic and serotoninergic activity in vitro. No long-term adverse effects have been noted when people chronically take it as an herbal antidepressant. However, certain St. John's Wort preparations have induced gastrointestinal disturbances.

Assessment of St. John's Wort. No research studies on St. John's Wort's effects on performance were found. Monitoring is advised.

CARBOHYDRATE SUPPLEMENTATION

There is evidence that consumption of additional carbohydrates (CHO) before, during, and after physical activity not only improves physical endurance capacity and endurance performance (Williams 1998), but also improves memory when blood glucose levels are restored to normal post-prandial levels in healthy elderly people (Manning et al. 1990). Whether or not a memory-enhancing effect occurs in young, active people is unresolved by research (TTCP 2001).

The mode of action for employing carbohydrate supplements is presumably through maintenance of blood glucose concentrations; glucose being the only fuel available for brain function, unless a person is fasting. To avoid gastrointestinal upsets resulting from high fiber intakes it is recommended that refined complex carbohydrates (e.g., white rice, white bread, and white pasta) and sugars provide some of the CHO. U.S. military nutritionists and medical researchers experimented with field rations in which soldiers take small quantities of CHO infrequently in the form of moderate (5% to 10%) solutions in water or as energy bars (consumed infrequently with water). These studies demonstrate that supplemental CHO can be efficacious if the activity involves a low level of physical work output (IOM-CMNR 2005). CHO feeding at a low level (e.g., 10 to 25 g/hour) is conjectured to lead to benefits in cognitive performance for many hours when physical work output is low. Such treatment protocols could pertain to commercial drivers as well, and ought to be researched for their potential application.

In terms of employing nutritional strategies to enhance sleep, there is some evidence that taking supplemental carbohydrates can be of assistance in managing one's sleep schedule. Caldwell et al. (2009) suggested that although eating a meal immediately before the sleep period is not recommended, it is important to maintain good nutrition at all times. If individuals eat immediately before sleep, they should favor grains, breads, pastas, vegetables, and fruits. They should also avoid large meals, high-fat meals, high-acid meals, and sweets. High carbohydrate (CHO) supplementation before bedtime has been associated with reduced amounts of wakefulness and stage 1 sleep, decreased stage 4 sleep, and increased rapid eye movement (REM) sleep (Porter and Horne 1981).

The somnolent effects of high CHO meals may depend in part on gender, age, and time of day of consumption (Spring et al. 1982). Afaghi et al. (2007) observed that a 90% CHO meal with a high glycemic index (GI) shortened sleep latency by 50% compared with a low glycemic index meal, and by about 40% when fed 4 h before sleep onset compared with 1 h before. Conversely, drowsiness may be offset immediately after high- and low-GI CHO intake; however, low-GI CHO intake may delay the onset of drowsiness (Landstrom et al. 2000). A comparison of low-fat, high-CHO meals to high-fat, low-CHO meals indicated that higher cholecystokinin (CCK) concentrations after high-fat, low-CHO meals were associated with greater feelings of sleepiness and fatigue (Wells et al. 1997).

Assessment of CHO Supplementation. Although it is still popularly believed that taking supplemental carbohydrates can help induce sleep (e.g., the Ehert diet for combating jet lag), the research evidence is too weak to suggest that the effects are worthy of pursuit. No recommendations beyond monitoring developments are made here.

AMINO ACIDS

There are numerous forms of amino acids; approximately 20 amino acids (organic compounds) occur naturally in animal proteins. Other amino acids are fabricated to be placed into commercially available dietary or nutritional supplements. Many amino acid supplements are used for purposes not particularly pertinent to the sleep induction or improved cognitive performance themes of this synthesis. Because most commercially available amino acid supplements seemingly have little effect on cognitive performance, they do not warrant much discussion in this report.

Tryptophan

The essential amino acid tryptophan, 5-Hydroxytryptophan (5 HTP), common in dietary protein, is available as l-Tryptophan, a dietary supplement sold in health food stores. Tryptophan has mild sedative-like effects and appears to induce drowsiness. Many people accept tryptophan as an aid to facilitate sleep.

Tryptophan inhibits gluconeogenesis, and probably induces drowsiness as a result of its ability to increase brain levels of serotonin (5-hydroxytryptamine: 5HTP, a calming neurotransmitter that in moderate levels appears to be involved in the regulation of alertness) and melatonin from the pineal gland (Wurtman et al. 1980). Serotonin has a relatively short half-life because it is rapidly metabolized by monoamine oxidase, and therefore l-tryptophan is likely to have limited efficacy. As for sleep induction, clinical studies have not clearly established tryptophan's effects on sleep itself.

Moja et al. (1984) demonstrated that pre-sleep ingestion of an amino acid mixture containing all essential amino acids caused a decrease in stage 4 sleep latency (fall into deep sleep faster) and an increase in stage 4 sleep duration during the first 3 h of sleep. The half-life of tryptophan is about 2 h; effects last about 4 h. The recommended dose is approximately 1 gram about 30 min before the desired sleep period. Depletion of tryptophan has also been observed to decrease stage 2 sleep, to increase wake time after sleep onset and rapid eye movement density, and to shorten the first and second REM period intervals (Voderholzer et al. 1998). Midmorning tryptophan depletion delays REM sleep latency during the following night's sleep (Arnulf et al. 2002). Tryptophan does not appear

to impair performance even immediately after administration (Lieberman 1989).

Other advocates touting tryptophan suggest it may increase the threshold of pain, or even reduce pain, and therefore may delay some forms of fatigue; but this has not been definitively demonstrated. Tryptophan has been widely employed as an antidepressant with few side effects. The metabolite of tryptophan 5-hydroxytryptophan (5-HTP) has been suggested to have effects similar to those of tryptophan (Wilson and Maughan 1992; TTCP 2001).

One widely held belief is that consumption of significant amounts of turkey meat (e.g., at Thanksgiving dinner) results in drowsiness attributable to high levels of tryptophan contained in the meat, levels that are actually comparable to that contained in many other meats. The explanation for Thanksgiving postprandial drowsiness is that it likely has more to do with the large meal consumed, including the turkey, carbohydrates, and alcohol, rather than attributing the drowsiness to the turkey meat itself.

Assessment of Tryptophan. There is no reported proven efficacy for tryptophan's purported benefits regarding cognitive performance enhancement (TTCP 2001). It appears it would not be worthwhile to propose more research on tryptophan for its potential use as a sleep inducer.

There is only scant evidence supporting ergogenic or cognitive benefits from most amino acids. There are some reports that amino acids such as bioglycin, a biologically active form of glycine, offer slight improvements in memory and attention (File et al. 1999). Branched Chain Amino Acids (BCAA) supplementation (e.g., tyrosine) can serve as energy for working muscles, and is said to reduce or delay the onset of central fatigue (Hassmen et al. 1994; Blomstrand et al. 1997; Struder et al. 1998; TTCP 2001). However, sufficient quantities of BCAA can actually be achieved through a balanced diet, and therefore taking supplements is not so important and actually may be a wasted effort. Doses of 6 g/day may offer lean body mass maintenance during times of stress. Doses of 5 to 20 g in pill form and 1 to 7 g of BCAA in liquid form have been found to be safe.

Tyrosine

Tyrosine, a protogenic amino acid, is one of the 20 amino acids used by the body's cells to synthesize proteins. The word "tyrosine" from the Greek tyros, meaning cheese, was first discovered in 1846 by von Liebig in the protein casein from cheese. Tyrosine is claimed to improve cognitive mental performance, improve mood and memory, and diminish symptoms in human subjects exposed to such stressors as cold, high altitude, or during periods of acute psychological and/or intense environmental stress. Thus, tyrosine is said to provide an increased ability to resist stress.

Tyrosine is a precursor of central and peripheral catecholaminergic neurotransmitters—dopamine and norepinephrine. Several studies administered 100 mg/kg of tyrosine taken in two 50 mg/kg doses over several hours. Based on pharmacokinetics, the duration of effect is estimated to be 4 to 6 h; however, there is insufficient behavioral data available. The ratio of tyrosine to other large neutral amino acids; that is, leucine, isoleucine, and valine is important. Tyrosine's effect is blocked if given with these other amino acids. No serious side effects have been reported during long-term tyrosine therapy for depression; but occasional gastrointestinal distress has been reported. Tyrosine may offer some value in treating stress response to severe exercise, whereas physical performance effects are relatively insignificant.

Evidence of tyrosine's effectiveness in stress resistance is equivocal. Positive articles in the literature include studies with military populations demonstrating tyrosine's utility during conditions of stress, cold, fatigue (Banderet and Lieberman 1989; Lieberman 1994; Deijen et al. 1999) and during prolonged work with sleep deprivation (Owasoyo et al. 1992; Neri et al. 1995; Magill et al. 2003). Cognitive performance and mood states may be improved during adverse exposures to cold and altitude, which may lead to an improvement in physical performance. In normal circumstances, tyrosine does not appear to have any significant effect on mood, or cognitive and physical performance (Thomas et al. 1999).

Assessment of Tyrosine. Although tyrosine may improve resistance to stress, and there is moderate rationale for reducing fatigue, the evidence for an effect on cognitive function is weak and conflicting. It is unlikely to be effective with acute treatment. Factors that need to be considered regarding taking supplemental amino acids are the dose level, optimal composition of the supplement, and optimal timing of ingestion in relation to exercise (Wolfe 2000).

Tyrosine has no direct ergogenic benefit on physical performance, but may indirectly enhance performance through cognitive or perceptual mechanisms. The extent of any benefits of taking supplemental amino acids such as tyrosine to reduce fatigue remains unresolved. Tyrosine is a potential candidate for further laboratory research, especially to confirm or not confirm its possible beneficial effects on cognitive performance (TTCP 2001).

MULTIVITAMIN SUPPLEMENTS

Good nutritional advice has always been to monitor one's dietary intake to ensure taking in sufficient quantities of vitamins and minerals, which should first be obtained in the normal daily diet as preventive medicine to preserve good health. The U.S. Army Center for Health Promotion and Preventive Medicine (U.S. Army CHPPM 2004) reminds us that a poor diet with a supplement is still a poor diet. The U.S. Department of Agriculture (USDA) publishes listings of

recommended Required Daily Allowances (RDA) of vitamins to maintain good health. Such RDA lists prompted generations of people to take supplemental multivitamins, especially in the one-a-day vitamin pill form, as common measures for prevention of health problems. Generally, this refers to persons taking daily a variety of vitamins in combination, in pill or capsule form (e.g., combinations of vitamin B complex, vitamin C, and E, and so on). Some people take large amounts of vitamins and minerals in hopes of obtaining an ergogenic effect. However, although the effects of nutrients obtained by eating food have been proven to assist in the regulation of normal cellular metabolism, ergogenic effects of vitamin and mineral supplements have not.

The Army recently employed the National Academy of Sciences' Institute of Medicine Committee on Military Nutritional Research (IOM-CMNR) to address issues of the use of dietary supplements by U.S. military personnel. One of the concerns raised was soldiers' excessive use of vitamins. Greenwood and Oria (2008) reported that eight surveys of military personnel depicted a high use of dietary supplements (as high as 60% of respondents in one survey reported using at least one supplement), especially vitamins and minerals, but also other supplements as well. Vitamins and minerals were used by about 45% of service members on active duty. Other popular dietary supplements in use were bodybuilding supplements (21%) and weight-loss products (18%). A call for similar survey data concerning the use of supplemental vitamins among commercial drivers may be warranted.

Among the numerous claimed benefits of taking multivitamins are: reduced depression, enhanced positive mental attitude (B-complex vitamin mixtures), enhanced physical endurance (B-complex vitamin mixtures), improved recovery from high-intensity activity (Williams 1989; Clarkson 1995), and maintenance of immunocompetence (mostly through antioxidants). There is some evidence for the potential of vitamins to contribute to reduction of depression and therefore promoting a more positive mental attitude (e.g., from cobalamin) (Applegate and Grivetti 1997). Most likely any effect of taking many of the supplemental vitamins is mediated through correction of subclinical deficiencies in the body, helping to enact corrections in vitamin deficiencies, wherein a person is/was already experiencing a shortfall of the body's required vitamins or enhancing energy release from metabolic fuels.

Balk et al. (2007) provided an extensive review of supplements of vitamins B-6, B-12, and folic acid, and concluded that the few available randomized controlled trials of the three supplements, alone or in combinations, do not provide adequate evidence for a beneficial effect of supplementation on cognitive function testing in people with either normal or impaired cognition. Although they may not be so clearly beneficial, *chronic supplementation* with low levels of vitamins (of the order of the RDA) is almost certainly without untoward effects. However, in general, the effectiveness of taking multivitamins is unresolved. Even the duration of supplemental vitamin effects is not so clear. In the cases of the B group vitamins and vitamin C, because excess water-soluble vitamins are excreted if not needed, any ergogenic effect may be only transient, persisting for hours rather than days following cessation of supplementation. Much of the supplemental vitamin compounds consumed are believed to just be sloughed off by the body's normal digestive processes. Taking a multivitamin does not make up for a diet lacking in nutrients. Taking multivitamins, like other dietary supplements, is meant to be a part of an overall healthy lifestyle (Neuhouser et al. 2009).

Assessment of Multivitamins. Ensuring that the body takes in adequate levels of vitamins and minerals is important in maintaining good health. The recommended way to do that certainly begins with following a good nutritional diet plan, something many commercial drivers have difficulty meeting (Roberts and York 2000; Krueger and Brewster 2002). Taking supplemental vitamins and minerals has not been sufficiently demonstrated to enhance either cognitive or physical performance as much as the technique may simply meet the body's needs not being met through good food nutrition intake. More research may be called for on the possible ergogenic effects of megadoses of B-complex vitamin mixtures, and on the potential of antioxidants to speed recovery from stressful expenditures of physical energy.

ANTIOXIDANTS TO FIGHT FATIGUE

Antioxidant supplements are meant to produce a reduction in free radical production, especially during exercise (Bucci 1993). Most antioxidants reduce lipid peroxidation. Vitamin C, for example, is thought to act in combination with glutathione to protect cellular membranes from oxygen radicals attaching at the surface of the membrane. Ingesting antioxidant vitamins C and E increases plasma concentration, but does not necessarily increase the total plasma antioxidant capacity. Although somewhat controversial, it has been argued that increasing antioxidant defense attenuates loss of muscle function associated with stiffness and soreness of untrained muscles that have been vigorously exercised.

In terms of antioxidants reducing oxidative stress and providing any cognitive benefits, some studies of middle-aged and elderly volunteers reported positive effects of antioxidant supplementation on performance during cognitive tests; however, these have not been replicated. The effects are not very likely to be found for normal younger individuals, especially with acute treatment.

Although beta-carotene is a powerful antioxidant, its effects on physical performance have not been adequately studied or reported. The antioxidant quercetin, a naturally occurring flavonoid found in a variety of plant products, including

blueberry, red onion and red apple skins, and kale, is reported to have antioxidant and free radical-scavenging properties that may enhance physical and cognitive performance, as well as some health and immunity benefits. Recent nutritional supplement advertising over the Internet, by a commercial vendor, employs one of the world's best known athletes (cyclist Lance Armstrong) to promote benefits of quercetin as allegedly being able to assist in fighting fatigue (without really addressing what is meant by fatigue). The vendor advertises quercetin in a nutritional liquid beverage and in a candy chew format. The advertising infers that U.S. Department of Defense (DoD) testing substantiated claims that products with quercetin in them help individuals fight fatigue. Indeed, DoD-sponsored physical and physiological experiments were conducted in university and military research labs to examine quercetin effects. However, the advantages of quercetin to date (Nieman et al. 2007, 2009) have largely been in protecting endurance athletes (Olympic-type cyclists, marathon runners, etc.) from the onset of upper respiratory infection (URI) after completing their endurance events.

U.S. Army biomedical researchers have been examining quercetin for possible applications of inserting it as an additive to food and field rations for soldiers and marines. However, a September 2008 blue ribbon nutrition research panel indicated that research has not fully established significant benefits of quercetin regarding cognitive performance or fatigue. Although quercetin is in an "interesting phase of nutritional development," and shows some potential, the evidence supporting its positive effects has not been solid enough to merit incorporation of quercetin as a ration component (Army Nutritional Science review, AIBS 2008).

Assessment of Antioxidants to Fight Fatigue. One of the principal reasons for reporting about quercetin here is that medical scientists, both within the DoD and as outside nutritional science reviewers, express concerns about the willingness of commercial vendors to overstate beneficial claims to nutritional supplements in their advertising, particularly over the Internet. It seems particularly egregious to attribute scientific support from DoD testing when those claims are overstated.

Internet caution: Much of what is advertised on the Internet has not been properly vetted for its veracity.

ANABOLIC STEROIDS

Androgenic anabolic steroids are analogs of testosterone used to promote gains in muscular strength and physical and muscular endurance. They are called anabolic because they increase protein synthesis through interaction with specific receptors in various tissues (Friedl 2002a, b). Androgens, dehydroepiandrosterone (DHEA) and androstenedione, the so-called sex steroids, are produced in the ovaries and adrenals for females, and in the testes and adrenals for males. There are no distinctly "male" or "female" hormones, but rather general differences in concentrations between genders. The ovaries are the primary source of estradiol and luteal phase progesterone. The adrenals are the chief source of DHEA and its sulfate ester DHEA-S. The ovaries and adrenals are the main source of androstenedione and testosterone. Male testes produce testosterone (McArdle et al. 1991). As a multi-functional steroid, DHEA has been implicated in a broad range of biological effects in humans and other mammals. Together with DHEA-S, it is the most abundant steroid in humans.

In the United States, DHEA, sold increasingly as a food supplement, has been popular with longevists and especially among body builders who take supplemental DHEA for muscle building, or by other athletes who take it as a performance enhancer. The mode of action is an increase in protein synthesis, inhibition of catabolic effects of glucocorticoids, and some effects on the CNS. It is difficult to determine an optimal dose for DHEA as there is wide variation in individual response. Most people who take DHEA report using a dose of 50 to 100 mg per day, usually cycled two weeks on DHEA and then one week off. Strength athletes often use DHEA in conjunction with anabolic/androgenic steroids, or immediately following a steroid cycle, to combat the steroid-induced reduction in endogenous testosterone production. Some studies show this to be effective for increasing lean body muscle size (mass), total testosterone, and improving muscle strength (Bowers 1999). To achieve the intended effects, chronic use over several weeks is required, combined with appropriate nutrition and physical training. In the presence of an adequate diet, anabolic/androgenic steroids can contribute to increases in body weight, often in lean mass (American College of Sports Medicine 1984).

It is claimed that DHEA promotes or enhances mood and well-being (Drake et al. 2000; Alhaj et al. 2006). However, cognitive and mental effects with steroids may be detrimental, as for example high levels of methyltestosterone (40 mg/day) have shown cognitive impairment (Su et al. 1993). Additionally, there is evidence that mood and behavioral disturbances can occur (Williamson and Young 1992). Arlt et al. (2000) indicated anecdotal reports of enhanced sexual drive, particularly among female users, and that DHEA also increased androstenedione levels. Wolf et al. (1997) and Wolf and Kirschbaum (2002) reported increased androstenedione levels with DHEA supplementation and no cognitive performance enhancement in older men and women.

A new Steroid Control Act in the United States effectively placed androstenedione under Schedule III of controlled substances beginning in January 2005. However, DHEA was not included in this act. In the United States, both DHEA and DHEA-S are readily available as over-the-counter nutritional supplements and have been advertised with claims that they may be beneficial for a wide variety of ailments (Calfee and Fadale 2006).

Assessment of Steroids. It appears that DHEA offers no demonstrated cognitive performance advantages. More

research is needed on DHEA to determine if its use is safe and whether or not it actually improves athletic or physical performance.

HYDRATION WITH WATER

Water is an absolutely essential nutrient with proven benefits to the body. Body fluid balance is maintained by signals from the hypothalamus, pituitary, and kidneys signaling thirst in response to dehydration or the production of urine in response to over-hydration. When workers or exercisers expend physical energy in hot environments, particularly hot-humid environments, there is always a concern that they do not become dehydrated. In addition to the normal loss of bodily fluids, sweat rates are noticeably higher in hot-humid environments, leading to a quicker loss of body water. In a few hours of intense exercise in the heat, water loss or dehydration can reach proportions that impede body heat dissipation and severely compromise cardiovascular function and work capacity. For an acclimatized person, water loss by sweating may reach a peak of about 3 liters per hour during very strenuous work, especially in the heat, and may average nearly 12 liters (about 26 lb) on a daily basis. As dehydration gradually progresses and plasma volume drops, sweating is reduced and thermoregulation becomes progressively more difficult (McArdle et al. 1991).

Maintaining a normal body water level (euhydration) delays psychological strain resulting from such environmental stressors as heat. A body water deficit of 3% to 4% of body weight will reduce sweat rates, elevate heart rate, and increase core body temperature as it is related to a reduction in both sweating and blood flow to the skin. For each 1% decrease in body weight attributable to dehydration, the heart rate increases four beats/min, core temperature increases by 0.15°C, and mean sweat rate decreases by 29 g/h. When water loss reaches 4% to 5% of body mass a definite impairment is noted in physical work capacity (McArdle 1991). These effects also combine to reduce the capacity of the brain to carry out cognitive functions. Gopinathan et al. (1988) found that dehydrated subjects demonstrated significant and progressive reductions in the performance of arithmetic ability, short-term memory, and visuomotor tracking at 2% or more body fluid deficit compared with the euhydrated state. That is, if an individual is 2% dehydrated, cognitive and physical performance may both be degraded, and significant impairments in performance occur as water loss continues past 4%.

The primary aim of fluid replacement is to maintain plasma volume so that circulation and sweating can progress at optimal levels (McArdle et al. 1991). The most effective defense against heat stress is adequate hydration. Physiologists, who champion proper water balance in the body, claim that the subtle cognitive benefits of proper hydration include good states of vigilance, alertness, memory, and problem solving. The benefits to performance continue while a state of euhydration is maintained.

Maintaining proper hydration (euhydration) is very important for commercial drivers, particularly truck drivers who engage in significant physical tasks including loading and unloading of freight, coupling trailers, and securing loads. Dehydration becomes a common circumstance while doing physical labor during late summer months in some geographic locations (e.g., the southeastern United States) where the ambient environment is not only hot, but accompanied by high humidity (~ >80%). Three to four hours of physical labor (e.g., loading or unloading one's truck) in such an environment can dehydrate a driver, and make him or her more fatigued and less alert when the driver resumes driving (Krueger and Van Hemel 2001). Adhering to a proper hydration schedule in such circumstances is important, and having a regular drinking plan to replenish lost body fluids is advised. The U.S. Army Research Institute of Environmental Medicine's (USARIEM) physiological research programs clearly demonstrate the best replacement for lost bodily fluids (hypohydration) is to regularly drink plain water.

Along with national trends, many commercial drivers now consume large quantities of bottled water, which seems inherently preferable to drinking numerous sugar-laden soft drinks containing caffeine and other substances. Some bottled waters contain small quantities of sodium, and if the water source is from springs, they may contain traces of minerals. Commercially bottled water does not provide the small quantities of fluoride that municipal tap water provides us. This may be a concern to those prone to teeth cavities. In some locales, caffeine-laced bottled water is readily available at truck rest stops and fast food stores.

If hyperhydration (too much body water) occurs, it is likely more attributable to the consumption of too many drinks (e.g., water, coffee, and soft drinks) while driving. An obvious effect here is a need to urinate more frequently. Monitoring urine coloration is important for ensuring proper hydration levels and kidney functioning. The U.S. military's preventive medicine guidance advocates that soldiers in field operations periodically take notice of the coloration of their expended urine as a check for proper hydration and kidney functioning. Urine which is repeatedly "too yellowed" is usually an indication of dehydration or improper kidney functioning (USA CHPPM and USARIEM regularly published preventive medicine guidance for military personnel).

The surveyed literature did not reveal whether the effects of commercial drivers not stopping frequently enough to perform this function has been assessed or reported. Good health and wellness practices dictate that commercial drivers maintain a proper level of euhydration by monitoring the amount of fluids (preferably water) they consume and eliminate (Krueger and Brewster 2002).

Assessment of Hydration. An abundance of significant physiological research has demonstrated the importance of maintaining good hydration levels (euhydration) in the body at all times (McArdle et al. 1991; Krueger 1993; USA CHPPM

and USARIEM, annually). Commercial drivers must be attuned to their hydration state, and they should follow a drinking plan to replace bodily losses of liquid through sweat, especially when doing strenuous work in hot, humid environments. Adequate levels of hydration can be maintained by drinking copious amounts of simple, clean drinking water.

FLAVORED VITAMIN WATERS

Beverage dealers now are marketing nutrient-laced, flavored drinks such as "vitamin water" products. The approach is to provide a vitamin-filled, lower-calorie specialized beverage advertised as being more healthful than the traditional ubiquitous colored and flavored soft drink sodas. Critics charge some of these more expensive premium "healthy" beverages have a lot of calories (albeit fewer than contained in soda soft drinks), but there is a lack of compelling evidence to back up suggestions that the products are actually good for consumers. There is little in the way of published research to suggest products such as Coca Cola's Glaceau Vitamin Water™ are a good way for the body to absorb vitamins.

From another point of view, it is arguable whether or not the nutritional possibilities of Vitamin Water™ constitute a large part of its popular appeal. Many consumers who purchase these newer products indicated that they are not overly concerned with assimilation of the vitamins, but simply drink Vitamin Water™ because they like its taste or that the drinks sound or appear to be more nutritious and less artificial than other sodas. Presumably, some people who drink these beverages may be drinking them in lieu of taking supplemental vitamins.

ELECTROLYTE REPLACEMENT DRINKS

These drinks, such as Gatorade®, are designed to replace the necessary electrolyte elements lost through perspiration. Such drinks are most effective when taken near the middle or at the end of lengthy exercise or endurance events such as running a marathon, because they can help maintain the balance of electrolytes in the body and restore homeostasis. For short exercise workouts, water will do just as well to replace lost body fluids, and water is much less expensive (physiologists at U.S. Army Research Institute of Environmental Medicine, Natick, Massachusetts: G. P. Krueger, personal communication, Nov. 2010).

WEIGHT LOSS DIETARY SUBSTANCES

Nutritionists, dieticians, and weight-loss experts advocate following healthy approaches to losing weight. In a preface to addressing supplemental dietary pills here, it warrants mentioning again. "There is no magic bullet for losing weight. The most effective way to lose weight and keep it off is through lifestyle changes. Eat healthy, low-calorie foods, watch portion sizes, and engage in regular physical activity. It is no magic pill, but it works" [www.MayoClinic.com (2010)].

Literally hundreds of weight-loss products (diet pills, powders, and liquids) are available in the commercial market place; obtainable in grocery stores, drugstores, health food stores; or advertised for sale in magazines and on the Internet. Advertising and sales outlets tout a confusing array of ingredients as being helpful for losing weight. Many people have experimented with different weight-loss supplements in search of something that appears to work for them. That time-consuming search engages people in much trial and error, is usually expensive and frustrating, and can even be dangerous to one's health.

Many providers of various products (diet pills, fat burners, etc.) attempt to inform consumers with useful information about: (a) efficacy—do the products work?, (b) safety, (c) information supplied by the FDA about the products, (d) the reputation of the company advertising the product, (e) guarantees and return policies, and (f) price and value. Most weight-loss products are touted to have significant physical effects on the body, but usually not much is written about whether or not the particular product(s) have an impact on cognition or on cognitive performance—one of the principal foci of this synthesis.

It is a challenge for consumers to determine which public information sources are credible or offer veracity in the descriptions or reports provided about diet pills (or other supplements) meant to assist in losing weight. It is difficult to determine whether or not a particular dietary product will be useful and whether or not it is good for the individual. Credible information sources can be found on the FDA website: http://www.fda.gov/cder/consumerinfo/weight_loss_products.htm or the Internet sites of reputable medical centers, such as the one on "Tools for Healthier Lives" on the website of the MayoClinic (see: www.MayoClinic.com, and click on weight loss). There are many other seemingly credible information sources, such as Dr. C. Everett Koop's Web MD site (www.webmd.com).

Assessment of Dietary Weight-Loss Products. There are literally hundreds of different dietary weight-loss products in the public marketplace. Because no credible scientific studies on the general class of dietary supplements are cited in this synthesis, it would be inappropriate to offer significant commentary on their efficacy for either weight-loss purposes or for sustaining or enhancing performance (physical or cognitive).

Additional caution and fat burners. For the consumer it is difficult to know what the contents are of the actual product one acquires, or even if the list of ingredients for a purchased item matches what actually is contained in the bottle. Many weight-loss pills contain a cocktail of ingredients, some with more than 20 herbs, botanicals, vitamins, minerals, or other add-ons, such as caffeine or laxatives. Just how these ingredients interact individually and collectively with people's bodies is largely unknown; and using them can be a risky venture, especially if a person is taking other medications as well [www.MayoClinic.com (2010)].

In this synthesis, the point has been made several times that dietary supplements, and therefore weight-loss aids too, are not subject to the same rigorous standards as are prescription drugs or medications sold over-the-counter with FDA approval. Weight-loss products are marketed while demonstrating only limited proof of effectiveness or safety. Without the authorization of the FDA, vendors can and do make health claims about products based on their own review and interpretation of their own research or by citing the research of outside organizations. If a product is proven to be dangerous, the FDA can announce it is "pulling a product off the market." However, such rare FDA action does not always bring about complete withdrawal of the product from the market place, and FDA actions appear to have minimal impact on what products continue to be advertised from overseas sources available over the Internet.

There is a class of diet pills that offer promise of quick weight loss that warrant special attention here. It can be said that "fat burners" (fast promise weight-loss diet pills) do at least two things. They act on the hypothalamus, the region of the brain that helps regulate appetite. They also cause release of certain brain chemicals that trigger the body's stress mechanisms (fight or flight response)—in effect, encouraging the body to burn extra calories to be able to respond to a physical or emotional threat. To stay ready for the attack that never comes, the body keeps burning calories even when the body is at rest. Previously, fat burners generally contained ephedrine, caffeine, and aspirin as their active ingredients. Beginning in 2004, after the FDA banned the use of ephedrine in diet pills in the United States, some manufacturers began using herbal ephedra or Ma huang. Others used citrus aurantium (CA) from mandarin oranges and green tea extract (GTE) (see: www.weightlossforall.com).

A sampling of popularly sold *fat burners* available as over-the-counter-weight-loss-pills, or on the Internet lists caffeine as a main ingredient as it is found in green tea extract. They also contain CA, ginkgo biloba, and Siberian ginseng. Other fast track weight-loss products also list as contents: Guarana, hoodia, HCA theanine (an amino acid in green tea), bitter orange (an "ephedra substitute"), and many other herbs. On its popular website, www.MayoClinic.com (2010), the Mayo Clinic lists 9 to 10 different ingredients commonly found in popular weight-loss pills, along with helpful commentary to inform the public about the efficaciousness and potential hazards of each substance. People with intentions of using such crash weight-loss products would do well to consult the Mayo Clinic's cautions.

On its website in January 2009, the FDA provided updated information to augment the "warning announcements" it made in December 2008 informing the public that the FDA had recently identified nearly 30 weight-loss, "natural fat buster" products, each of which may contain unlisted and possibly dangerous ingredients such as sibutramine, a powerful Schedule IV controlled substance anti-obesity prescription drug, as well as a laxative drug (phenolphthalein) suspected as a carcinogen. The FDA identified other substances found in such dietary pills; but indicated none of the offending chemicals were listed as contents on the products. Additionally, according to the FDA, some of the products originating in Asia, but which are being marketed in the United States as dietary supplements are of concern because they contain potentially harmful contaminants. [Source: www.fda.gov weight-loss products]. For *the latest FDA Consumer information* announcements about drugs and supplements in the marketplace, consult the FDA website at: http://www.fda.gov/cder/consumerinfo/DPAdefault.htm.

APPENDIX D

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APPENDIX E

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Abbreviations used without definitions in TRB publications:

AAAE	American Association of Airport Executives
AASHO	American Association of State Highway Officials
AASHTO	American Association of State Highway and Transportation Officials
ACI–NA	Airports Council International–North America
ACRP	Airport Cooperative Research Program
ADA	Americans with Disabilities Act
APTA	American Public Transportation Association
ASCE	American Society of Civil Engineers
ASME	American Society of Mechanical Engineers
ASTM	American Society for Testing and Materials
ATA	Air Transport Association
ATA	American Trucking Associations
CTAA	Community Transportation Association of America
CTBSSP	Commercial Truck and Bus Safety Synthesis Program
DHS	Department of Homeland Security
DOE	Department of Energy
EPA	Environmental Protection Agency
FAA	Federal Aviation Administration
FHWA	Federal Highway Administration
FMCSA	Federal Motor Carrier Safety Administration
FRA	Federal Railroad Administration
FTA	Federal Transit Administration
HMCRP	Hazardous Materials Cooperative Research Program
IEEE	Institute of Electrical and Electronics Engineers
ISTEA	Intermodal Surface Transportation Efficiency Act of 1991
ITE	Institute of Transportation Engineers
NASA	National Aeronautics and Space Administration
NASAO	National Association of State Aviation Officials
NCFRP	National Cooperative Freight Research Program
NCHRP	National Cooperative Highway Research Program
NHTSA	National Highway Traffic Safety Administration
NTSB	National Transportation Safety Board
PHMSA	Pipeline and Hazardous Materials Safety Administration
RITA	Research and Innovative Technology Administration
SAE	Society of Automotive Engineers
SAFETEA-LU	Safe, Accountable, Flexible, Efficient Transportation Equity Act: A Legacy for Users (2005)
TCRP	Transit Cooperative Research Program
TEA-21	Transportation Equity Act for the 21st Century (1998)
TRB	Transportation Research Board
TSA	Transportation Security Administration
U.S.DOT	United States Department of Transportation