Schedule II Opioids and Stimulants:

Opinions of the Medical Expert Panel regarding Commercial Driver Performance and Crash Risk

Presented to the Federal Motor Carrier Safety Administration

Panelists

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acclaro Research Solutions, Inc.

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Executive Summary

FMCSA partnered with Acclaro Research Solutions, Inc. (Acclaro) to conduct a systematic review of the literature and to identify relevant studies addressing how the licit use of prescribed schedule II opioids and stimulants may impact the risk of commercial motor vehicle (CMV) crashes or indirect measures of CMV driver performance. Acclaro convened a Medical Expert Panel to discuss and review these findings. This report provides the panel's opinions on this topic for consideration by FMCSA's Medical Review Board.

For opioids, it is the opinion of the panel that the licit use of schedule II opioids conveys at least a moderate increased risk for fatal accident involvement, injury accident involvement, and crash causation. There is some information from laboratory testing suggesting that opioids may impact driving-related abilities; however, the evidence is insufficient to determine whether the use of opioids causes impairment on indirect measures of driving performance. Population data suggest that chronic use of opioids is likely to lead to dose escalation and possibly iatrogenic dependence/addiction over time; the panel believes conditions requiring chronic opioid treatment may be incompatible with the routine successful completion of driving tasks.

In the opinion of the panel, the licit use of stimulant medication for ADHD likely reduces the increased crash risk associated with ADHD, though timing of stimulant dosing can be complex and positive effects are limited to the time during which the medicine is present at therapeutic levels. In the opinion of the panel, the use of amphetamines, which are highly addictive, outside of closely monitored ADHD treatment poses a substantially increased crash risk. The effects of the licit use of stimulants for ADHD treatment are unlikely to change significantly with chronic use.

For both opioids and stimulants, the panel believes the effects of licit use cannot be determined by serum levels, and effects will vary across individuals based on metabolism and other pharmacokinetic factors. As with any drug, there are likely to be drug-drug interactions with both opioids and stimulants; however, research studies have not addressed these effects due to various complications. The panel also believes that throughout the literature, research findings underestimate the actual impact of the use of both opioids and stimulants.

The panel expressed the opinion that there are other medications that may significantly impact CMV drivers that are not well studied in the literature to date. They suggest and that additional studies would be beneficial to evaluate these substances.

Introduction

The primary mission of the Federal Motor Carrier Safety Administration (FMCSA) is to reduce commercial motor vehicle crashes, injuries, and fatalities. As a part of this mission, its Medical Programs Division works to ensure that commercial motor vehicle (CMV) drivers engaged in interstate commerce are physically qualified and able to safely perform their work. In order to improve safety, FMCSA commissions systematic reviews on a variety of topics. These findings, together with input from Medical Expert Panels, are used to inform policy and decision-making.

A systematic review of the current literature investigating the impact of the licit use of Schedule II opioids and stimulants on CMV driver safety was completed by Acclaro Research Solutions, Inc. The findings from this research were compiled in an evidence report, *Schedule II Opioids and Stimulants & CMV Crash Risk and Driver Performance: Evidence Report and Systematic Review.*

A Medical Expert Panel was convened on July 8, 2014 to discuss this evidence report. The panel's main goal was to provide opinions to the Medical Review Board that will aid in their decision-making process.

Members of the panel received an electronic version of the evidence report prior to the meeting, and were asked to review the document and arrive at the meeting with questions and opinions on the evidence.

The Medical Expert Panel meeting was held in the offices of FMCSA at Department of Transportation headquarters, located in Washington, DC.

Agenda for Medical Expert Panel Meeting

The meeting commenced at 9:00 AM with introductions of all the attendees. Following the introductions, Elaine Papp, Division Chief of Medical Programs at FMCSA, provided background information on FMCSA and the Medical Review Board process, outcomes from previously held MEP meetings, detailed information on the purpose of the meeting, as well as expected goals of the session. Acclaro then presented their findings from the evidence report.

After Acclaro's presentation of findings, the Medical Expert Panel began their discussion of the evidence report as a whole as well as the methodology and findings

for each research question. During the discussion, Acclaro team members recorded key points of the discussion and various opinions of the panelists and compiled them into draft opinion statements. Once discussion on each research question came to a close, Acclaro team members reviewed the opinion statements. Panelists came to agreement amongst themselves as to the final wording and content of each opinion statement.

The session culminated with a discussion of Acclaro's next steps, as well as next steps of the Medical Expert Panel, and concluded at 5:00pm

Attendees

Medical Expert Panel

Mitchell A. Garber, MD, MPH, MSME, Senior Managing Consultant, Engineering Systems, Inc.

Tara Gomes, MHSc, Assistant Professor, University of Toronto, Canada

Gary G. Kay, PhD, President, Cognitive Research Corporation and Associate Professor, Georgetown University School of Medicine, Washington, DC

Nicholas Lomangino, MD, Acting Manager, Medical Specialties Division, Office of Aerorspace Medicine, Federal Aviation Administration

Carl A. Soderstrom, MD, Chief, Medical Advisory Board, Maryland Motor Vehicle Administration

Federal Motor Carrier Safety Administration

Elaine Papp, Division Chief, Medical Programs

Angela Ward Wongus, RN, Nurse Consultant and COR, Medical Programs Division

Eileen Nolan, Nurse Consultant

Acclaro Research Solutions, Inc.

Katherine Fiedler, PhD, Program Manager

Christine Brittle, PhD, Principal Investigator

Chris Cotterman, Associate Research Analyst

Jacquelyn Palmer, Associate Research Analyst

Evidence Report

The panel discussed the findings from a systematic evidence report prepared by Acclaro Research Solutions, Inc. (Acclaro) under contract DTMC75-13-R-00007 to the Federal Motor Carrier Safety Administration (FMCSA). The report addressed several key research questions:

1. What is the relationship between licit use of prescribed schedule II opioids or stimulants and:

a) **Risk of a motor vehicle crash?**
b) **Indirect measures of driver performance, including impaired cognitive and/or psychomotor functions (measured using driving simulators and Psychomotor Vigilance Tasks (PVT))?**

2. Are the effects (as found in question 1) of licit use of prescribed opioids or stimulants measureable by serum levels? Do these effects remain consistent or vary based on metabolism or other pharmacokinetic parameters?

3. Do the effects (as found in question 1) worsen or improve when: 1) drug-drug interactions take place with other schedule II medications or over-the-counter medications; or 2) the drug has been chronically administered over a period of time (stable use)?

To identify relevant studies, Acclaro searched several large databases (Academic Search Premier, Business Source Complete, the Cochrane Library, CINAHL, Embase, Health Business Elite, the National Guideline Clearing House, PubMed, Proquest Research Library, Science Direct, and TRID). Acclaro also identified relevant unpublished reports by searching the websites of various governmental, commercial, and non-profit organizations. The references of identified materials were also searched.

Databases were searched using a set of identified keywords. Abstracts were reviewed against a set of *a priori* retrieval criteria, and then the full text of potentially relevant items was reviewed against a set of defined inclusion criteria. All studies which met the criteria were abstracted and included in the review.

A total of n=48 relevant studies were identified via the search process.

The report reached the following conclusions:

Research Question	Conclusions
1a	• There is moderate evidence to support the contention that licit use of opioids increases the risk of a motor vehicle crash. • There is weak evidence to support the contention that licit use of stimulants increases the risk of a motor vehicle crash.
1b	• There is moderate evidence that licit use of opioids negatively impacts indirect measures of driver performance. • There is weak evidence that licit use of stimulants positively impacts indirect measures of driver performance among drivers with ADHD based on consistent findings among a small number of studies. • There is moderate evidence that licit use of stimulants has minimal or positive indirect measures of driver performance among drivers taking low doses of stimulants.
2	• There is moderate evidence that the effects of opioids and stimulants are measureable by serum levels.
3	• The evidence pertaining to whether schedule II opioids and stimulants interact with other schedule II or prescription medications is unacceptably weak. • There is moderate evidence that stable use of schedule II opioids is associated with reduced negative impacts. • The evidence pertaining to whether chronic use of stimulants impacts driving or driving related skills is unacceptably weak.

Opinions from the Medical Expert Panel

Initial Opinions

The following opinions from the Medical Expert Panel were stated as a preamble to the research questions. These opinions apply to all of the research questions below.

- We recognize that driving complexity is increased in Commercial Motor Vehicles (CMVs) compared to non-commercial passenger vehicles and that the outcomes of CMV crashes pose significantly greater potential for adverse outcomes.
- The severity of the underlying condition for which medication is being prescribed should be considered when determining whether an individual is deemed medically fit to operate a CMV.
- The pressures of commerce make it difficult for CMV drivers to self-regulate their driving while using medications. Behavior that reduces potential exposures (e.g., avoiding traffic, driving only during the day, only taking familiar routes, or not driving entirely) is generally not an option that is available to CMV drivers who must drive as a condition of their occupation.

- The panel noted that additional relevant studies would have been identified and included had more general search terms (such as "cogn*" or "psychomotor") been utilized in the review of the literature. The search terms utilized by the Acclaro team were more specific in nature.

The effects identified in the literature likely represent the minimum effects of medications. Studies conducted on this topic cannot effectively mimic actual dosing, real use patterns, CMV driving conditions, or situations that often lead to accidents.

Question 1a

What is the relationship between licit use of prescribed Schedule II opioids or stimulants and risk of a motor vehicle crash?

Opioids

- Use of licit opioids conveys at least a modest increased risk for fatal accident involvement, injury accident involvement, and crash causation. These risks appear to rise as prescribed dose increases.

Stimulants

- Licit use of stimulant medicine for treatment of ADHD likely reduces the increased crash risk associated with ADHD. However, timing of stimulant dosing in ADHD patients can be complex, and risk may remain elevated in treated ADHD patients at times when stimulant activity is absent or waning.
- Amphetamines and similar stimulants have a very high tendency for abuse.
- Use of amphetamines outside of closely monitored treatment of ADHD poses a substantially increased crash risk.

Question 1b

What is the relationship between licit use of prescribed Schedule II opioids or stimulants and indirect measures of driver performance, including impaired cognitive and/or psychomotor functions (measured using driving simulators and psychomotor tests)?

Opioids

- Although there is some information from laboratory testing to suggest that opioids may impact driving related abilities, the evidence is insufficient to determine whether use of opiate medication causes impairment on indirect measures of driver performance. Most studies have investigated single, acute, low doses of these medications with young, healthy subjects. The tests used in

these studies have failed to adequately assess essential driving ability domains. Most of the measures are brief in duration and therefore do not address critical abilities such as vigilance or sustained attention. Studies that have used high fidelity driving simulators or 'on-the-road' driving tests have failed to show impairment in maintenance of lane position following administration of opioids. However, in these studies the driving challenges encountered by the subjects when driving may have been inadequate to detect a change in crash likelihood or other performance deficits.

Stimulants

- Licit use of stimulant medicine for treatment of ADHD has been repeatedly shown to improve the driving performance of treated subjects. However, the beneficial effects are limited to the time during which the medicine is present at therapeutic levels. In addition, caution must be exercised to avoid the medication adversely effecting normal sleep; insomnia is a very common adverse event which could result in a performance deficit in driving due to sleep loss.
- Schedule II stimulants are not appropriate as an occupational counter-fatigue measure.

Question 2

Are the effects of licit use of prescribed opioids or stimulants measureable by serum levels? Do these effects remain consistent or vary based on metabolism or other pharmacokinetic parameters?

- The effects of licit use of opioids and stimulants cannot be determined by serum levels; however, very high serum levels are likely indicative of tolerance or substance use disorders. The pharmacodynamics effects do not remain consistent; they vary by metabolism and other pharmacokinetics. They also vary considerably across individuals. There does not appear to be any data suggesting a minimum threshold level or time-course for impairment. This applies to the entire period of drug exposure from onset, to peak, to withdrawal.

Question 3

Do the effects of licit use of prescribed opioids or stimulants worsen or improve when:

- **Drug-drug interactions take place with other Schedule II medications or over-the-counter medications?**
- **The drug has been chronically administered over a period of time (stable use)?**

Drug-Drug Interactions

- As with any drug, there are likely to be drug-drug interactions. Research studies have not addressed the effects of these interactions with Schedule II drugs due to logistical and other complications.
- While it is certainly true that not all combinations of drugs can be analyzed, a review of dispensing data (e.g., IMS databases) may indicate specific combinations of drugs that are frequently co-prescribed and which may merit further investigation.

Stable Use

- Chronic use of opioids in the community does not equate to stable use of the medications. Opioids are typically prescribed for use as needed (PRN) and are often titrated to pain level, which may vary substantially over time. Population data suggest that chronic use of opioids is likely to lead to dose escalation over time and possibly iatrogenic dependence/addiction. There is limited evidence that impairment resulting from stable opioid use diminishes over time. However, the studies that examined this issue failed to establish a safe level of use at the level of the individual.
- Conditions requiring chronic opioid treatment may be incompatible with commercial motor vehicle operations.
- The effects of the licit use of stimulant medication for the treatment of ADHD are unlikely to be significantly changed due to chronic use, although users may experience periodic dose adjustments. Following such a dose adjustment, a period of assessment with regard to adverse effects might be required. Other use of stimulants is associated with a potential for substance use disorder.

Opportunities for further research

There are medications that may be having a significant impact on the CMV driver population, given their common utilization in the United States, but which are not well-studied in the literature reviewed to date. We recommend that further review of the scientific literature be completed, and in many cases, additional studies be funded, to evaluate the impact of the following medications on CMV driver safety:

- Benzodiazepines
- Diphenhydramine and other first generation antihistamines
- Non-schedule II stimulants, including phentermine, modafinil and armodafanil
- Prescription opiates most commonly utilized in the US, including: oxycodone, hydrocodone, and meperidine, among others

These studies might use research questions similar to the current Comprehensive Evidence Report.

Additional research avenues to consider

- Examine the patterns of actual use of medications and how this impacts CMV driver safety.
- Examine the hypothesis that CMV drivers with ADHD have decreased crash risk with amphetamine use.
- Examine the safety implications for individuals withdrawing from stimulants used for the treatment of ADHD. Are performance deficits evident at the end of the shift? Are performance deficits evident the following day due to secondary insomnia?
- Examine the effects of shorter acting and longer acting amphetamines, including patterns of use and impact on alertness.
- Examine the use patterns of stimulants. Are drivers using amphetamines for weight loss? Are CMV drivers using phentermine to lose weight?

It is the opinion of the MEP that many of the studies of opioids and stimulants that are needed to fully understand the safety implications for CMV drivers are not being funded by traditional sponsors. The panel urges FMCSA to collaborate with NHTSA, NIDA and the DOT Office of Drug and Alcohol Policy and Compliance to facilitate the funding and execution of this important research.

Appendices

Appendix 1: Agenda

Item
Meeting kickoff, introductions, & agenda
Presentation of research findings
Q1a discussion
Q1b discussion
Q1b discussion
Q2 discussion
Q3 discussion
Discussion and review of recommendations
Next steps and action items

Appendix 2: Medical Expert Panelist Biographies

Mitchell A. Garber, MD, MPH, MSME, Senior Managing Consultant, Engineering Systems, Inc.: Dr. Garber has over 20 years of military and civilian experience in transportation accident investigation. He was the first and only full-time Medical Officer at the U.S. National Transportation Safety Board and participated in over 1000 investigations in all transportation modes. Dr. Garber has also presented testimony to Congress regarding medical issues in transportation accidents. He is a Member and Fellow of the Aerospace Medical Association, and member of the American Society of Safety Engineers, Human Factors and Ergonomics Society, Association for the Advancement of Automotive Medicine, and the American College of Occupational and Environmental Medicine. He has numerous educational and technical presentations and publications related to pathology, toxicology, human performance, and biomechanics in accident investigation. Dr. Garber specializes in medical analysis, transportation policy, human factors and ergonomics, accident investigation and reconstruction, biomechanics, and injury causation.

Tara Gomes, MHSc, Assistant Professor, University of Toronto, Canada: Tara Gomes is the Scientific Lead and co-Principal Investigator of the Ontario Drug Policy Research Network (ODPRN), a provincial network of researchers with expertise in pharmaceutical utilization, outcomes and policy with the key objective of rapidly

conducting relevant pharmacoepidemiology research for provincial decision-makers to inform drug policy in Ontario. In particular, her research is focused on using Ontario's large health administrative databases to conduct observational drug utilization and safety research timely, relevant and responsive to drug policy-makers' needs.

Tara Gomes is an Assistant Professor at the Institute for Health Policy, Management and Evaluation and the Leslie Dan Faculty of Pharmacy at the University of Toronto, and a Scientist at the Li Ka Shing Knowledge Institute of St. Michael's Hospital and the Institute for Clinical Evaluative Sciences.

Gary G. Kay, PhD, President, Cognitive Research Corporation: Dr. Kay is an Associate Professor of Neurology at Georgetown University School of Medicine, where he was the former Director of Neuropsychology. He currently serves as the President of Cognitive Research Corporation, a Saint Petersburg, Florida based contract research organization. He is the author and developer of the CogScreen computerized cognitive test battery. His research has focused on evaluating the impact of drugs and neurological conditions on human performance using computer-based cognitive testing and driving simulation. He serves as a consultant to government agencies and to the pharmaceutical industry, and he has been an invited speaker at professional meetings across the globe including meetings addressing guidelines and methodology for evaluating the effect of medications and diseases on driving and flight performance. He is the co-author of the National Highway Transportation Administration publication, *Drugged Driving Expert Panel Report: A Consensus Protocol for Assessing the Potential of Drugs to Impair Driving*. He has published peer-reviewed articles that have appeared in *Journal of the American Geriatrics Society*, *Archives of Internal Medicine*, *American Psychologist*, *Human Psychopharmacology*, *Annals of Allergy*, *British Journal of Urology*, *European Urology, British Journal of Pharmacology*, and *American Journal of Managed Care*. He is an author and the co-editor of *Aeromedical Psychology*, published in 2013.

Nicholas Lomangino, MD, Deputy Division Manager, FAA Medical Specialties Division, US Department of Transportation: Dr. Lomangino is board certified in Internal Medicine. He has vast experience and practice in aerospace medicine, emergency medical services, and occupational and environmental health. Dr. Lomangino served as Chief of Flight Medicine in the U.S. Air Force and as a Regional Flight Surgeon for the FAA. Dr. Lomangino is currently a physician tasked with formulating and implanting new policies for airmen and air traffic control specialists

(ATCSs) for the FAA. He has been instrumental in the development of the new FAA Sleep Apnea Policy and serves as a drug and alcohol rehabilitation program subject matter expert for the FAA's Office of Aerospace Medicine. Dr. Lomangino is a certified Medical Review Officer and an Associate Fellow of the Aerospace Medical Association (AsMA).

Carl A. Soderstrom, MD, Chief, Medical Advisory Board, Maryland Motor Vehicle Administration: Dr. Carl A. Soderstrom is an Adjunct Professor of Surgery at the University of Maryland School of Medicine and is a Senior Volunteer Staff member of the school's National Study Center for Trauma and EMS.

Dr. Soderstrom has served and continues to serve on local, regional, and national committees, societies, and task forces addressing issues related to injury prevention. He served as President of the Association for the Advancement of Automotive Medicine from 2008 to 2010. Appointed by the Secretary of Transportation, Dr. Soderstrom recently completed service on the Medical Review Board (MRB) of the Federal Motor Carriers Safety Administration (2009 –2012). Currently, Dr. Soderstrom is a member of the Transportation Research Board's (National Research Council) Safe Mobility for Older Persons Committee and it joint Sub-Committee, Medical Advisory Boards and Driver Licensing.

Dr. Soderstrom continues to teach at the Shock Trauma Center and at the Schools of the University of Maryland and to undertake and assist on research projects at the National Study Center. He is a member of the Center's Crash Injury Research and Engineering Network (CIREN) team. In addition, he is a Faculty Associate at the Johns Hopkins University Bloomberg School of Public Health Department of Health Policy & Management.