Schedule II Opioids and Stimulants & CMV Crash Risk and Driver Performance

Evidence Report and Systematic Review

Prepared for the Federal Motor Carrier Safety Administration
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Table of Contents

List of Tables

List of Figures

Executive Summary

Introduction

Driving a large commercial truck is dangerous work. Truck drivers have a fatal work injury rate of 22.1 per 100,000 workers, the eighth highest in the nation.[1] According to the Federal Motor Carrier Safety Administration (FMCSA), large trucks were involved in 3,568 fatal crashes in 2011, killing 4,108 people and costing the U.S. $39 billion.[2]

The primary mission of the FMCSA is to reduce these 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 the FMCSA commissions systematic reviews on a variety of topics. These findings, together with input from FMCSA's Medical Expert Panel, are used to inform policy and decision-making.

This systematic review focuses on the effects that licit use of prescribed Schedule II drugs have on the risk of CMV crashes or on indirect measures of driver performance.

Schedule II drugs includes a variety of stimulants (such as amphetamine, methamphetamine, and methylphenidate), depressants (such as pentobarbital, glutethimide, and phencyclidine), and a large number of opioids (including codeine, morphine, hydrocodone, oxycodone, and methadone). While these substances have acceptable medical uses, they also carry high potential for impairment and abuse. This report focuses specifically on the effects of licit use of Schedule II stimulants and opioids.

Research Questions

FMCSA has identified the following research questions for this study:

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))?

[1] Source: Bureau of Labor Statistics: Census of Fatal Occupational Injuries, data for 2012, accessed February 2014: http://www.bls.gov/iif/oshwc/cfoi/cfch0011.pdf

[2] Source: FMCSA: Commercial Motor Vehicle Facts, March 2013, accessed February 2014: http://www.fmcsa.dot.gov/documents/facts-research/CMV-Facts.pdf

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?
3. Do the effects 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)?

Search Methodology

To identify relevant findings, Acclaro Research Solutions, Inc. (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 this review.

Findings for each identified study are presented and summarized by research question, along with a characterization of whether the identified evidence is strong, moderate, weak, or unacceptably weak.

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

Table 1: The criteria for each qualitative evidence rating

Strong	Evidence supporting the qualitative conclusion is convincing. It is highly unlikely that new evidence will lead to a change in this conclusion.
Moderate	Evidence supporting the qualitative conclusion is somewhat convincing. There is a small chance that new evidence will overturn or strengthen our conclusion.
Weak	Although some evidence exists to support the qualitative conclusion, this evidence is tentative and perishable. There is a reasonable chance that new evidence will either overturn or strengthen our conclusions.
Unacceptably Weak	Although some evidence exists, the evidence is insufficient to warrant drawing an evidence-based conclusion.

Findings

Research Question 1a

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

The evidence base for Question 1a consists of n=25 studies. Findings include n=17 original research articles and n=8 systematic reviews.

> **There is moderate evidence to support the contention that licit use of opioids increases the risk of a motor vehicle crash.** Several large and recent studies link opioid use to increased risk of driver fatalities, driver injury, crash risk, and unsafe driver actions. Most identified studies show increased risk. However, many of the findings are drawn from the same large European dataset, and many of them also classify all opioids together. Results for specific opioids are more limited and less convincing.
>
> **There is weak evidence to support the contention that licit use of stimulants increases the risk of a motor vehicle crash.** Most of the available evidence pertains to amphetamines and comes from a large European study which showed an increased risk of driver fatalities, driver injury, and crash risk. The use of stimulants to address driver medical conditions such as ADHD may improve driver crash risk based on one small study. Further research is required.

Research 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 Vigilance Tasks (PVT))?

The evidence base for Question 1b consists of n=29 studies. Findings include n=20 original research articles and n=9 systematic reviews.

> **There is moderate evidence that licit use of opioids negatively impacts indirect measures of driver performance.** Studies generally found indicators of impairment, especially for drug-naïve individuals. Impairment was most pronounced on psychomotor vigilance tasks related to pertinent driving skills such as attention, vision, auditory perception, and reaction time. Fewer studies included driving simulators or roadside driving tests; however, where these tests were included, findings tended not to be significant. Findings vary across drug and dose.

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. The handful of relevant studies generally found that stimulants improve performance among adults with ADHD on psychomotor vigilance tests related to reaction time and complex tasks, as well as performance in a driving simulator related to speeding and weaving.

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. The handful of relevant studies generally found limited or no negative outcomes and some small improvements in psychomotor vigilance tasks related to reaction time, coherence, car-following, accuracy, and speed. Effects tend to be dose specific, and may only be present for the use of small or moderate doses. Results were mixed as to whether stimulants can help to counter the effects of sleep deprivation.

Research 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 evidence base for Question 2 consists of n=14 studies. Findings include n=10 original research articles and n=4 systematic reviews.

There is moderate evidence that the effects of opioids and stimulants are measureable by serum levels. Findings were generally consistent across studies that serum levels are comparable to other methods in investigating relationships between licit drug use and driving impairment. However, this relationship likely exists for only certain Schedule II medications, and may also be subject to floor or ceiling effects. Investigating relationships by serum level allows for a better understanding of possible variation due to differences in how individuals metabolize medicines.

Research 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)?**

The evidence base for Question 3 consists of n=19 studies. Findings include n=12 original research articles and n=7 systematic reviews.

The evidence pertaining to whether Schedule II opioids and stimulants interact with other Schedule II or prescription medications is unacceptably weak. Limited data investigates the question of interactions, and what data do exist, conflict. Findings are likely drug and dose specific, and an insufficient evidence base exists at this time to adequately address the question.

There is moderate evidence that stable use of Schedule II opioids is associated with reduced negative impacts. Consistent data suggest that the negative impacts of opioids on driving and driving related skills diminish over time when doses remain stable. This is not the case for positive impacts, such as those that may be associated with methadone maintenance treatments. However, negative effects of opioids may still remain, even in chronic users.

The evidence pertaining to whether chronic use of stimulants impacts driving or driving related skills is unacceptably weak. A limited evidence base makes it difficult to draw conclusions on this topic.

Preface

Introduction

Driving a large commercial truck is dangerous work. Truck drivers have a fatal work injury rate of 22.1 per 100,000 workers, the eighth highest in the nation.[3] According to the Federal Motor Carrier Safety Administration (FMCSA), large trucks were involved in 3,568 fatal crashes in 2011, killing 4,108 people and costing the U.S. $39 billion.[4]

The primary mission of the FMCSA is to reduce these 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 the FMCSA commissions systematic reviews on a variety of topics. These findings, together with input from FMCSA's Medical Expert Panel, are used to inform policy and decision-making.

This systematic review focuses on the effects that licit use of prescribed Schedule II drugs have on the risk of CMV crashes or on indirect measures of driver performance.

Schedule II drugs includes a variety of stimulants (such as amphetamine, methamphetamine, and methylphenidate), depressants (such as pentobarbital, glutethimide, and phencyclidine), and a large number of opioids (including codeine, morphine, hydrocodone, oxycodone, and methadone). While these substances have acceptable medical uses, they also carry high potential for impairment and abuse. This report focuses specifically on the effects of licit use of Schedule II stimulants and opioids.

Purpose of Report

The focus of this study is 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 driver performance. The Federal Motor Carrier Safety Administration (FMCSA) has contracted Acclaro Research Solutions, Inc. (Acclaro) to conduct a systematic review of the literature and identify relevant studies that address this topic.

This report addresses the following questions:

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

[3] Source: Bureau of Labor Statistics: Census of Fatal Occupational Injuries, data for 2012, accessed February 2014: http://www.bls.gov/iif/oshwc/cfoi/cfch0011.pdf

[4] Source: FMCSA: Commercial Motor Vehicle Facts, March 2013, accessed February 2014: http://www.fmcsa.dot.gov/documents/facts-research/CMV-Facts.pdf

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)?

Report Organization

This evidence report and systematic review contains four major sections:

1) Background information on CMVs and Schedule II opioids and stimulants
2) Comparison of Relevant Regulations
3) Methodology
4) Evidence Summary

The Background section briefly summarizes the Controlled Substances Act and the five schedules of controlled substances, describes Schedule II substances and the medical conditions they are used to treat, and briefly discusses the prevalence and incidence of use of Schedule II opioids and stimulants.

The Comparison of Relevant Regulations provides relevant information on current federal regulations for CMV drivers and offers equivalent standards from four English-speaking countries as a comparison. Additionally, equivalent regulations from the Federal Aviation Administration (FAA), the Federal Railroads Administration (FRA), the Maritime Administration (MARAD), the Pipeline and Hazardous Materials Safety Administration (PHMSA), and the Federal Transit Administration (FTA) are summarized, providing a view of how licit use of prescription drugs is treated in the wider transportation industry.

The Methodology section describes in detail the sources that were searched, as well as the search terms used for each research question and the overall evidence base. This section also describes the evaluation criteria for determining the quality of the evidence for each study.

Finally, the Evidence Summary provides a detailed description of the evidence base for each research question, and includes summaries for each included study, grouped by question.

Report Funding and Role of Funders

This review was funded via contract DTMC75-13-R-00007 from the Federal Motor Carrier Safety Administration (FMCSA). FMCSA reviewed the report and provided comments. However, all research was conducted independently by Acclaro Research Solutions, Inc. and all findings are our own.

All authors declare no financial or other conflicts of interest.

Background

Schedule II Drugs

The Controlled Substances Act (CSA) became law in 1970, enacted as Title II of the Comprehensive Drug Abuse Prevention and Control Act. With this legislation, the United States established a federal drug policy to regulate the manufacture, importation, possession, and distribution of certain substances.

Under the CSA, five classifications of controlled substances--called schedules—were created, along with varying criteria to determine in which particular schedule a substance would be placed. Substances are classified based their potential for abuse, accepted medical use within the United States, as well as any applicable international treaties. The Department of Justice and the Department of Health and Human Services are typically responsible for adding or removing a specific substance from a schedule, though substances have also been scheduled through legislation passed by Congress. The current criteria for each schedule are shown in Table 2, below (source http://www.justice.gov/dea/docs/drugs_of_abuse_ 2011.pdf).

Table 2: Criteria for U.S. drug schedules

Schedule I	▪ The drug or other substance has a high potential for abuse. ▪ The drug or other substance has no currently accepted medical use in treatment in the United States. ▪ There is a lack of accepted safety for use of the drug or other substance under medical supervision.
Schedule II	▪ The drug or other substance has a high potential for abuse. ▪ The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions. ▪ Abuse of the drug or other substance may lead to severe psychological or physical dependence.
Schedule III	▪ The drug or other substance has less potential for abuse than the drugs or other substances in Schedules I and II. ▪ The drug or other substance has a currently accepted medical use in treatment in the United States. ▪ Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.
Schedule IV	▪ The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule III. ▪ The drug or other substance has a currently accepted medical use in treatment in the United States. ▪ Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III.
Schedule V	▪ The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule IV. ▪ The drug or other substance has a currently accepted medical use in treatment in the United States. ▪ Abuse of the drug or other substances may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule IV.

Unlike substances classified as schedule I, controlled substances in Schedule II have a medical application, though like schedule I substances they also carry a high risk for both physical and psychological dependence. Schedule II includes a variety of stimulants (such as amphetamine, methamphetamine, and methylphenidate), depressants (such as pentobarbital, glutethimide, and phencyclidine), and a large number of opioids (including codeine, morphine, hydrocodone, oxycodone, and methadone). This report focuses specifically on the effects of licit use of Schedule II stimulants and opioids.

Stimulants

Stimulants are a class of psychoactive substances that temporarily increase mental and physical functions, such as heart rate, blood pressure, respiration, concentration, and wakefulness. Schedule II stimulants are prescribed and legally used to treat a variety of conditions, including ADHD (Attention Deficit Hyperactivity Disorder), narcolepsy, and obesity. Commonly prescribed Schedule II drugs include amphetamine (Adderal, Dexedrine) and methylphenidate (Ritalin, Concerta). Methamphetamine and cocaine are also Schedule II stimulants and have approved, though limited, medical uses.

Opioids

Opioids are a class of psychoactive chemicals derived naturally from the opium poppy, or synthetically designed to produce similar effects. Unlike stimulants, opioids are depressants, and decrease mental and physical functions. Schedule II opioids are predominantly prescribed and used for the treatment of chronic pain, and include drugs such as morphine, codeine, oxycodone, and hydrocodone. Other uses include cough suppression (codeine and hydrocodone) and treatment of drug addiction and dependence (methadone).

Prevalence and Incidence of Licit Schedule II Drug Use

Use of prescription drugs of all types is increasing. In the period between 1988 and 1994, 39.1% of the population reported using at least one prescription drug in the past 30 days; that number increased to 47.5% for the period between 2007 and 2010.[5] Among therapeutic classes treated by prescription drugs, pain and ADHD represent a large number of total prescriptions, with 465 million and 78 million dispensed prescriptions, respectively.[6]

Regulatory Review

FMCSA Regulations

FMCSA regulations establishing the physical qualifications of CMV drivers can be found in 49 Code of Federal Regulations (CFR) 391(b) (1-13). Under these regulations, CMV drivers may not use any drug or substance that is "Schedule I, an amphetamine, a narcotic, or other habit forming drug" unless "the use is prescribed by a licensed medical practitioner…who is familiar with the driver's medical history and has advised the driver that the substance will not adversely affect the driver's ability to safely operate a commercial motor vehicle" (§391.41 (12)(i-ii)). Because many commonly-prescribed Schedule II drugs are amphetamines, narcotics and derivatives, their use while operating a CMV requires consultation with a medical practitioner and a prescription for use.

Comparative Analysis for Other Nations

Like the United States, many other nations consider the impairing effects of medications when determining a driver's fitness. When looking at other major English-speaking nations, Canada, the United Kingdom, Australia, and New Zealand all consider the effects of licit use of prescription drugs on driver fitness, and all prohibit driving while impaired by the use (licit or illicit) of prescription drugs. All five nations direct medical practitioners to consider

[5] Source: CDC/NCHS, National Health and Nutrition Examination Survey: http://www.cdc.gov/nchs/data/hus/2012/091.pdf
[6] Source: Source: IMS Health, National Prescription Audit, Dec 2012: http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Corporate/Press%20Room/2012_U.S/Top_Therapeutic_Classes_Dispensed_Prescriptions_2012.pdf

the possible impact of a drug on driving ability before issuing a prescription. With the exception of the United Kingdom, all nations specifically define categories of drugs that carry a risk of impairment; Canada and Australia offer further information about risks, as well as information for medical practitioners to consider when making a determination. A brief summary of national regulations is presented in Table 3, below.

Table 3: Comparison of national regulations as they relate to driving while using prescription drugs

	United States	Canada	United Kingdom	Australia	New Zealand
Addresses use of prescription drugs while driving	●	●	●	●	●
Defines drugs and substances that pose risk of impairment	●	●		●	●
Prohibits impaired driving	●	●	●	●	●
Advises consultation with medical practitioner	●	●	●	●	●
Provides information about risks and/or guidance for medical practitioners		●		●	

Sources: http://www.fmcsa.dot.gov/rules-regulations/administration/fmcsr/fmcsrruletext.aspx?reg=391.41 (United States); http://ccmta.ca/en/publications/resources-home/category/medical-standards-for-drivers (Canada); https://www.gov.uk/current-medical-guidelines-dvla-guidance-for-professionals (UK); http://austroads.com.au/images/stories/assessing_fitness_to_drive_2013_rev2.pdf (Australia); http://www.nzta.govt.nz/resources/medical-aspects/ (New Zealand)

Comparative Analysis for Other Modes of Transportation

Federal regulations establish similar controls for other modes of commercial transportation. Pilots and flight crews, railroad workers, and merchant marines are all permitted to use prescription drugs while on duty, provided the drug does not cause impairment. Both the Federal Aviation Administration (FAA) and Federal Railroad Administration (FRA) require a medical consultation to determine if the use of a drug is safe; the FAA additionally requires special, individualized disposition for use of some drugs. The Pipeline and Hazardous Materials Safety Administration (PHMSA) and the Federal Transit Administration (FTA) have no regulations regarding licit drug use. However, in 2002 the FTA published the *Prescription Over-the-Counter Medication (Rx/OTC) Toolkit*[7] in response to recommendations by the National Transportation Safety Board (NTSB); this document offers education and guidance on safety risks associated

[7] http://transit-safety.volpe.dot.gov/publications/substance/RxOTC/RxOTC_April2011_Feb2012_Update.pdf

with use of prescription drugs by transit employees. No agency maintains a list of explicitly banned licit drugs. Table 4, below, summarizes regulations for each industry.

Table 4: Comparison of federal regulations regulating licit use of drugs in various transportation modes

	FMCSA	Railroad	Air	Merchant Marine	FTA	PHMSA
Use of prescription drugs permitted	●	●	●	●	NSR	NSR
Impaired operation prohibited	●	●	●	●		
Medical consultation required	●	●	●			
Special disposition required for use of drugs			●			

NSR- No Specific Regulation
Sources: 49 CFR 219 (Railroad); 14 CFR 61, 67, 91 (Air); 33 CFR 95 (Merchant Marine); CFR 391(b) 1-13 (FMCSA)

Research Methodology and Evidence Base

Research Questions

FMCSA has identified several research questions for this study, which we have refined and further subdivided into discrete research questions to focus our search strategies. These questions are:

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)?

Sources Searched

We searched thousands of peer-reviewed journals using precisely defined key search terms to locate materials for this study. We searched the following electronic databases:

- **Academic Search Premier:** Full-text publications from all academic areas of study, including the sciences, social sciences, humanities, and medical sciences
- **Business Source Complete:** Full-text business publications and hundreds of scholarly, peer-reviewed journals covering all aspects of business
- **The Cochrane Library:** A collection of six databases that contain high-quality information to inform healthcare decision-making, including:
    - Cochrane Database of Systematic Reviews
    - Cochrane Central Register of Controlled Trials
    - Cochrane Methodology Register
    - Database of Abstracts of Reviews of Effects
    - Health Technology Assessment Database
    - NHS Economic Evaluation Database
- **Cumulative Index to Nursing & Allied Health (CINAHL):** Over 700 journals on topics related to nursing and allied health
- **Embase (Excepta Medica):** An index to pharmacological and biomedical literature from over 6,500 journals from 70 countries, including most MEDLINE records
- **Health Business Elite:** Articles in management, medical, general business, and industry specific topics
- **National Guideline Clearinghouse (NGC)**: Designed to provide physicians and other health professionals with an accessible mechanism for obtaining information on clinical practice
- **PubMed**: The National Library of Medicine's MEDLINE and PreMEDLINE databases; MEDLINE encompasses information from Index Medicus, Index to Dental Literature, and International Nursing Index, as well as other sources of coverage in the areas of allied health, biological and physical sciences, humanities and information science as they relate to medicine and health care
- **Proquest Research Library:** Indexing, abstracting, and many full-text entries for over 2,800 scholarly and general-interest periodicals; covers a very broad range of topics and sources
- **Science Direct:** Web database for scientific research that contains abstracts, tables of contents, and full text of Elsevier journal articles mainly in science and medicine, with some coverage of social sciences and humanities, particularly business, economics and psychology
- **TRID**: More than one million records related to worldwide transportation research

In addition, we also searched the "grey literature," which consists of unpublished reports, studies, and other materials which are not commercially available. We sought out these materials by searching the Web sites of various Federal agencies, as well as related commercial and non-profit organizations. We searched:

- American Academy of Pain Medicine http://www.painmed.org/
- American Association of Pharmaceutical Scientists (AAPS) http://www.aaps.org/PharmRes/
- American College of Occupational and Environmental Medicine http://www.acoem.org/default.aspx
- American Pain Society http://www.americanpainsociety.org/
- American Society of Health-System Pharmacists http://www.ashp.org/
- American Trucking Association http://www.truckline.com/
- Commercial Vehicle Safety Alliance http://www.cvsa.org/home.php
- Driving under the Influence of Drugs, Alcohol and Medicines (DRUID) http://www.druid-project.eu
- DOT Bureau of Transportation Statistics http://www.rita.dot.gov/bts/
- Federal Motor Carrier Safety Administration http://fmcsa.dot.gov/
- Food and Drug Administration http://www.fda.gov/
- International Council on Alcohol, Drugs, and Traffic Safety http://www.icadts.nl/
- International Narcotics Control Board http://www.incb.org/
- International Pharmaceutical Federation (FIP) http://fip.org/
- National Transportation Safety Board http://www.ntsb.gov/
- Parenteral Drug Association http://www.pda.org/default.aspx
- PhRMA, the Pharmaceutical Research and Manufacturers of America http://www.phrma.org/
- Transportation Research Board http://www.trb.org/Main/Home.aspx

Finally, we fully reviewed the references of retrieved articles in order to locate any additional relevant materials.

Search Terms Used

We searched for information using a set of specific keywords and text word combinations. These search terms varied according to our key questions and the sources being searched. All searches included both a "Schedule II" term and a "CMV/Driver" term. These terms were used in combination with terms for Question 1a, Question 1b, Question 2, and Question 3. Search terms are presented in Table 5 below.

All searches were limited to the English language. For databases where large numbers of results were returned (e.g., Science Direct) search terms were further limited to header/subject/keywords. Searching was done in November and December 2013.

Table 5: Search Terms

Schedule II Terms	("opioid" OR "opioids" OR "opiate" OR "opiates" OR "opium" OR "pain medicine" OR "narcotic analgesic" OR "narcotic analgesics" OR "pain reliever" OR "stimulant" OR "stimulants" OR "dextroamphetamine" OR "methamphetamine" OR "methylamphetamine" OR "amphetamine" OR "methylphenidate" OR "pemoline" OR "phenmetrazine" OR "lisdexamfetamine" OR "methylamine")
CMV/Driver Terms	("trucking" OR "commercial motor vehicle" OR "CMV" OR "commercial driving" OR "driving" OR "auto" OR "automobile" OR "driver" OR "motor vehicle")
Q1a Terms	("traffic accident" OR "automobile accident" OR "motor vehicle accident" OR "traffic crash" OR "automobile crash" OR "motor vehicle crash" OR "traffic related injury" OR "traffic injury" OR "automobile injury" OR "motor vehicle injury")
Q1b Terms	("potentially driver-impairing" OR "PDI" OR "drug driving" OR "drugged driving" OR "impaired driving" OR "drug-impaired driving" OR "drug impairment" OR "driving ability" OR "driving performance" OR "simulated driving" OR "driver simulator" OR "fitness to drive" OR "driver fitness" OR "psychomotor performance" OR "psychomotor effects" OR "cognitive function" OR "cognitive functioning" OR "cognition" OR "physiologic reaction" OR "vision" OR "motor function" OR "Psychomotor Vigilance Tasks" OR "Psychomotor Vigilance Task" OR "PVT")
Q2 Terms	("serum" OR "serum concentration" OR "plasma concentration" OR "drug concentration" OR "blood concentration" OR "maximum concentration" OR "Cmax" OR "metabolism" OR "pharmacokinetic")
Q3 Terms	("drug interaction" OR "drug interactions" OR "drug-drug interaction" OR "drug-drug interactions" OR "adverse reaction" OR "adverse reactions" OR "complication" OR "complications" OR "side effect" OR "side effects")

Complete sample search terms for the database PubMed appear as Appendix A to this report.

Reviewers read the title and abstract for each article, and decided whether to retrieve it in full-text using the retrieval criteria described in Appendix B which were established *a priori*. If an article met the retrieval criteria, it was retrieved in full-text and added to a reference manager program (Zotero) for additional analyses. Items were not added if they were already in the reference program; many items were identified in multiple sources.

Once all searching was complete, the items were again reviewed (this time using full-text) against a set of inclusion criteria which appear as Appendix C to this report. Reviewers made a decision about whether each article should be included or excluded. In cases of uncertainty, the article was flagged for follow-up and reviewed by the Principle Investigator. Where articles were excluded, reviewers also made a notation summarizing the reason for exclusion.

As a part of this process, reviewers were also asked to identify potentially relevant references in the identified studies. Reference items were retrieved and reviewed following the same

procedures analyzed above. Studies were also reviewed against a list of qualifying Schedule II opioids and stimulants (see Appendix D).

Evaluation of Quality of Evidence

Once the final set of articles was identified, each included article was reviewed for quality based on the standards used by the Cochrane Bias Method Group. Articles that shared a common data collection effort were treated as one unit for the purposes of this analysis.

Original research articles were given a bias rating (high risk, low risk, or unclear risk) on each of seven domains (see http://bmg.cochrane.org/assessing-risk-bias-included-studies). These domains are:

- **Selection bias/random sequence generation:** This reflects whether subjects between groups are systematically different; randomization mitigates against selection bias.
- **Performance bias/allocation concealment:** This reflects whether subjects between groups are systematically different in the care provided or in other interventions of interest. Blinding of participants and personnel mitigates against this risk.
- **Detection bias/blinding of participants and personnel:** This reflects whether participants and personnel know assignment to condition. Blinding or masking reduces the risk of this bias.
- **Detection bias/blinding of outcome assessment:** This reflects whether systematic differences between groups are present in how outcomes are determined. Blinding or masking of outcome assessors reduces the risk of this bias.
- **Attrition bias/incomplete outcome data addressed:** This reflects whether there are systematic differences between groups on withdrawal rates.
- **Reporting bias/selective reporting:** This reflects whether there are systematic differences between reported and unreported findings.
- **Other biases:** These reflect other potential areas of concern in study design, implementation, analysis, or reporting.

Using this method, studies are not given an overall score, but are rated separately in each domain.

Systematic review articles were ranked on a similar (but not identical) scale, using the same rankings (high risk, low risk, unclear risk). Categories included:

- **Inclusion criteria appropriate and specified in advance:** This reflects whether the study defined and used *a priori* selection criteria.
- **Search procedures appropriate and followed:** This reflects whether the study defined and used *a priori* search criteria.
- **Conflict of interest:** This reflects whether the study authors had or reported conflicts of interest.
- **Included studies grading for quality:** This reflects whether included studies were graded for quality.

- **Reporting of individual study results:** This reflects whether the results from each included study are summarized or available for review.
- **Selective reporting:** This reflects whether there are systematic differences between reported and unreported findings.
- **Other biases:** These reflect other potential areas of concern in study design, implementation, analysis, or reporting.

Statistical Methods

Identified data were reviewed by question topic and sub-topic. Data were abstracted by members of the research team and reviewed by the Principle Investigator. For each original research study data were gathered on the location of the study, design of the study, objective, procedures and protocol, sample size and demographics, included drugs and dose, overall conclusions, and specific findings. For systematic reviews information was recorded on study objective, sources and years searched, included drugs and doses, overall conclusions, and specific findings.

Insufficient data were available to conduct a meta-analysis, so findings are discussed qualitatively. The overall rating of each finding is rated as strong, moderate, weak, or unacceptably weak (see Table 1 for additional information).

Overall Evidence Base

A total of n=48 relevant studies were identified via our search process. These studies were identified via database searches, Web site searches, and reference list searches. The entire search process is diagrammed below in Figure 1.

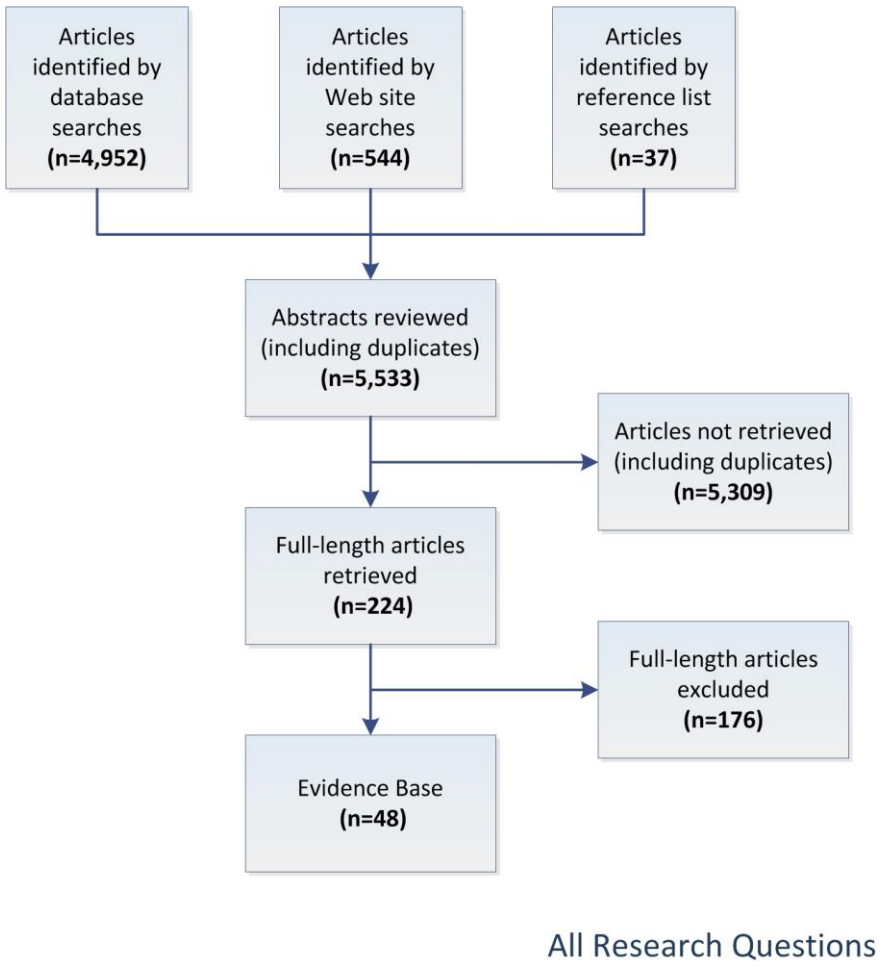


Figure 1: Evidence base, all questions

Evidence Summary

This section of the report presents findings for each research question. Each section first presents findings from relevant original research articles (n=37 across all questions) followed by relevant findings from literature reviews (n=11 across all questions).

Research Question 1a

Question 1a asks: What is the relationship between licit use of prescribed Schedule II opioids or stimulants and risk of a motor vehicle crash?

Evidence Base for Question 1a

The evidence base for Question 1a consists of n=25 studies, as shown in Figure 2. Findings include n=17 original research articles and n=8 systematic reviews.

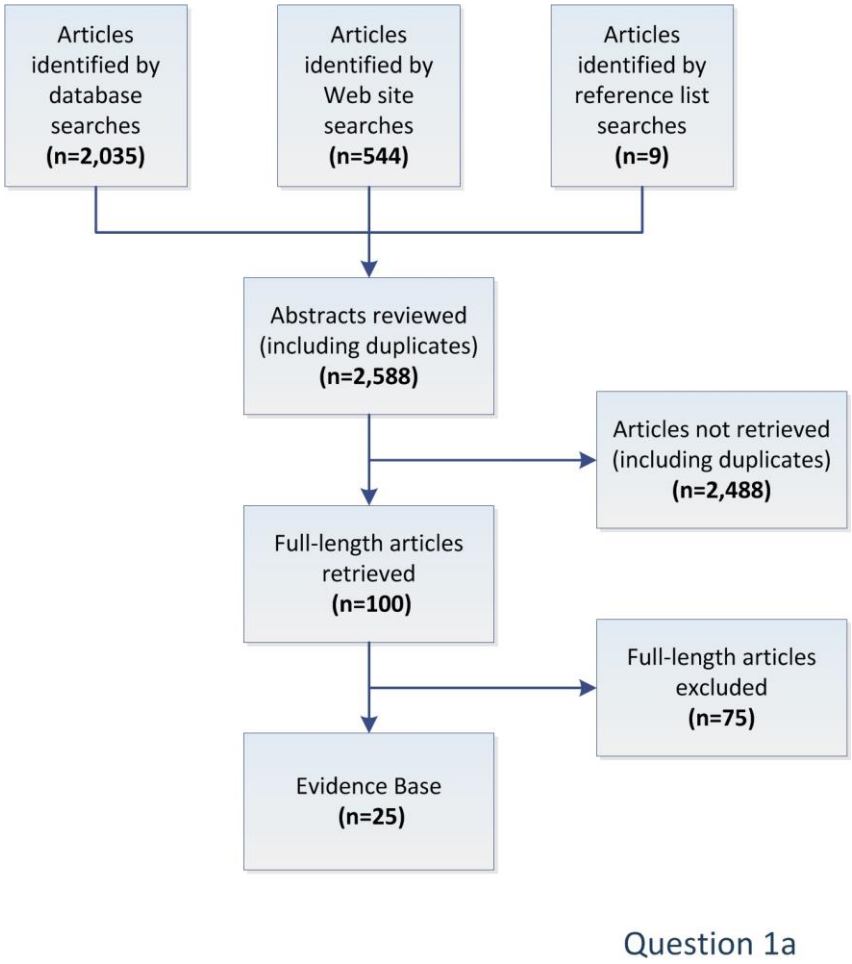
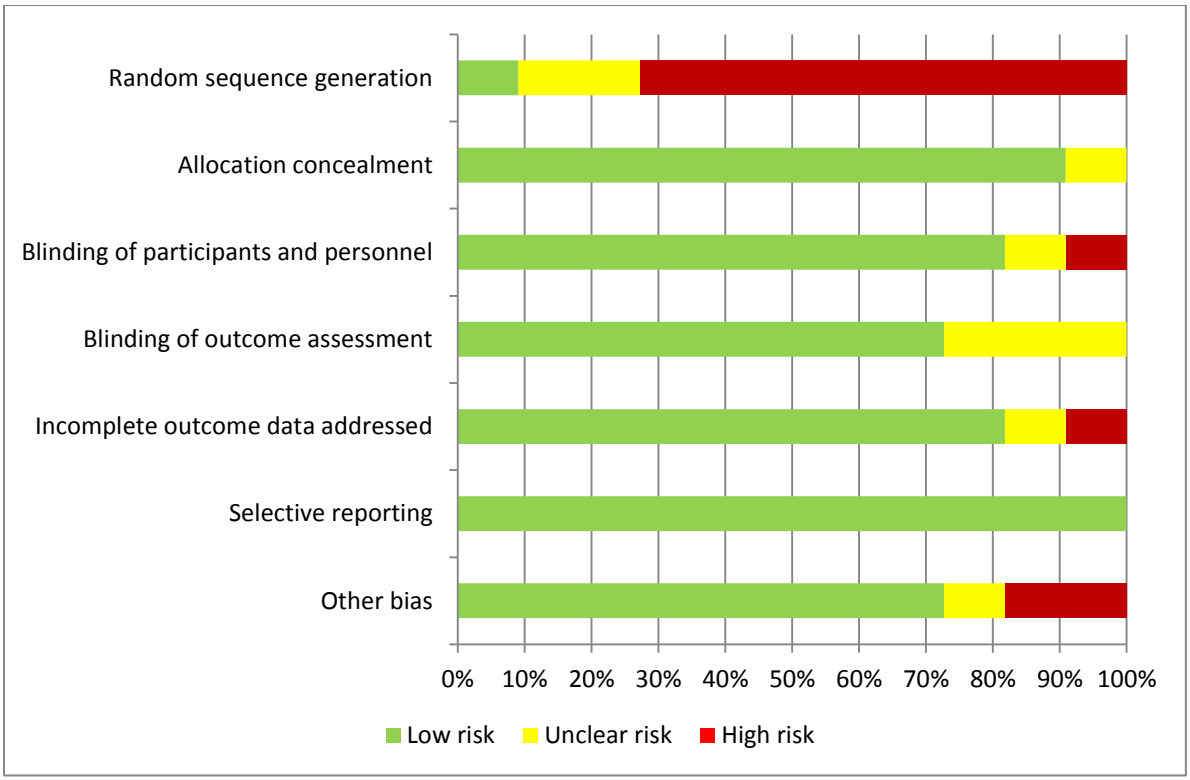


Figure 2: Evidence base, Question 1a

Quality of Included Studies

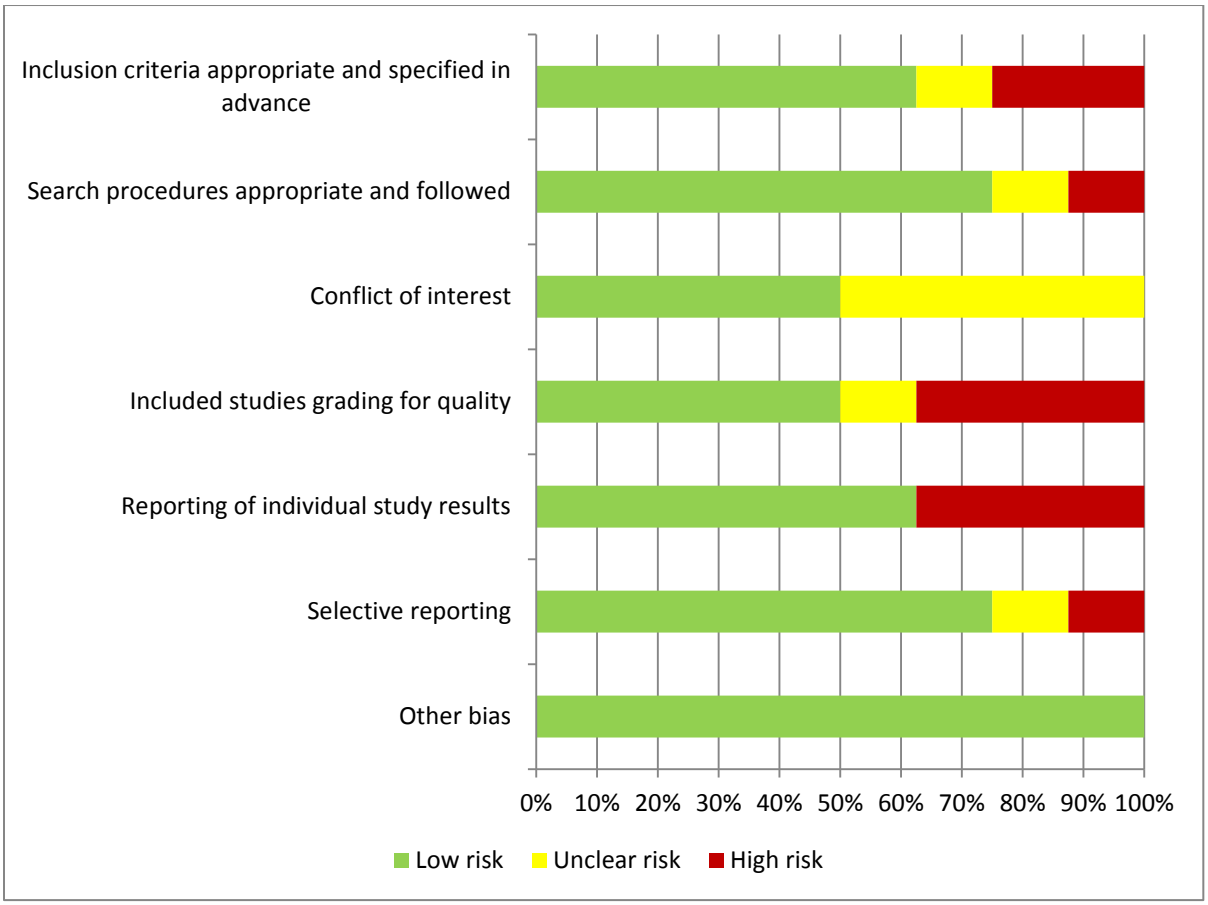
Each identified item was ranked for quality using the categories described in the research methodology section. The ratings for the original research articles are presented in Table 6. Generally, study quality was acceptable on all measures. However, the Q1a studies were of lower quality related to random sequence generation – this is because many of the studies were registry-based or used another design where drug use was not assigned but occurred naturally.

Table 6: Study Quality for Q1a Original Research Articles



The systematic review articles are of moderate quality, as shown in Table 7. About a third of the articles did not report results for each included study, nor did they do any grading on study quality.

Table 7: Study Quality for Q1a Systematic Review Articles



Summaries of Included Studies

Original research articles that address Q1a are shown in the tables below. Table 8 shows information about the study design and conclusions for original research studies. Table 9 shows detailed findings for each of the original research articles. The eight studies that share a common data collection effort are grouped together: one group of three studies, and one group of five studies.

Table 8: Study Design and Conclusions for Original Articles that Address Q1a

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Bachs et al. (2009) [1]	Norway, Cohort study	Examine the risk of a driver being involved in a road traffic accident while using codeine	Analysis of prescription drug dispending records and automobile crash records over a 33-month study period. Data from Norwegian Prescription Database (NorPD), the Norwegian Road Accident Registry, and the Norwegian Central Population Registry. Calculated Standardized Incidence Ratio (SIR), taking sex and age into consideration.	n=3.1 million; all inhabitants of Norway 18+ living in Norway 2004–2006 were included	Codeine (two groups 60 DDD (defined daily dose) or more, <60DDD)	SIR for codeine consumption is elevated and highest for those 35-54 and for high consumers; however, this decreases when co-prescriptions are excluded
Bramness et al. (2012) [2]		Examine the risk of a driver being involved in a road traffic accident while using methadone			Methadone (liquid formulation)	Men exposed to methadone appear to have an increased risk of being involved in motor vehicle accidents involving personal injuries; this increased risk could not be explained by exposure to benzodiazepines
Engeland et al. (2007) [3]		Examine the risk of a driver being involved in a road traffic accident while using natural opium alkaloids			Natural opium alkaloids	The risk of being involved in an accident as a driver was markedly increased in users of natural opium alkaloids
Bernhoft et al. (2012) [4]	Europe, Case-control Study	Assess the risk of driving while using medicinal drugs by comparing injured/killed drivers to drivers	Fourteen hospitals located in six European countries provided information on injured and killed drivers, including blood and saliva samples (cases). Blood and	n=2,490 (injured drivers, Maximum Abbreviated Injury Scale ≥ 2); n=1,112 (killed	Medicinal opioids (detected at a threshold equal to or above equivalent cutoffs for blood/saliva)	Driving while taking medicinal opioids or amphetamines elevates the risk of being severely injured or killed in a crash

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
		participating in a roadside survey	saliva samples were also collected from drivers via roadside surveys in locations near these hospitals (controls).	drivers); n=50,000 (roadside survey drivers)	Amphetamines (detected at or above 20 ng/mL in whole blood or 360 ng/mL in saliva)	
Hels et al. (2013) [5]		Assess the risk of driving while using medicinal drugs by comparing injured/killed drivers to drivers participating in a roadside survey	Fourteen hospitals located in six European countries provided information on injured and killed drivers, including blood and saliva samples (cases). Blood and saliva samples were also collected from drivers via roadside surveys in locations near these hospitals (controls).	n=2,490 (injured drivers, Maximum Abbreviated Injury Scale ≥ 2); n=15,832 (roadside survey drivers)	Medicinal opioids (detected at a threshold equal to or above equivalent cutoffs for blood/saliva)	Driving while taking medicinal opioids or amphetamines elevates the risk of being severely injured or killed in a crash; it's unclear why men are at lower risk, but it may be due to women's smaller body sizes or tendency to drive smaller vehicles
					Amphetamines (detected at or above 20 ng/mL in whole blood or 360 ng/mL in saliva)	
Hels et al. (2012) [6]		Assess the risk of driving with alcohol, illicit drugs and medicines in various European countries	Fourteen hospitals located in six European countries provided information on injured and killed drivers, including blood and saliva samples (cases). Blood and saliva samples were also collected from drivers via roadside surveys in locations near these hospitals (controls).	n=2,490 seriously injured drivers; n=1,112 killed drivers; n=15,832 control drivers for seriously injured; n=21,917 control drivers for killed	Medicinal opioids (Morphine, Codeine, Methadone, Tramadol)	Common odds ratio of getting seriously injured/killed when driving while positive for medicinal opioids is significantly above 1 and of the order of about 5-8 (medium increased risk); true for several countries
					Amphetamines	Common odds ratio of getting seriously injured when driving while positive for amphetamine was significantly increased, and the overall risk is expected to be significantly increased of the order of at least 5 (medium increased risk); around 25 for getting killed (highly increased risk)

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Kuypers et al. (2012) [7]	Belgium, Case-control study	To calculate the odds of having a motor vehicle accident after using medicinal opioids and amphetamines	Blood samples were taken from drivers that were seriously injured in a motor vehicle accident and were then compared to blood samples taken from drivers in areas nearby the hospitals where patients were admitted.	n= 337 cases (patients admitted to 1 of 5 hospitals from a motor vehicle crash); n=2,726 control drivers in randomly chosen areas near each hospital	Medicinal opioids (Morphine, Codeine, Methadone, Tramadol)	Adjusted risk of driving under the influence of medical opiates is not statistically significant, but did show a slight trend towards increased risk
					Amphetamines	Crude risk of driving under the influence of amphetamines is higher
Van der Linden et al. (2013) [8]		Compare blood concentrations of opioids and amphetamines in seriously injured drivers to non-injured drivers to assess the effects of these drugs	Blood samples were taken from drivers that were seriously injured in a motor vehicle accident and were then compared to blood samples taken from drivers in areas nearby the hospitals where patients were admitted.	n=377 (cases, seriously injured drivers); n=2,750 (controls, roadside respondents)	Codeine	No significant difference
					Methadone	There was a trend for methadone, indicating possibly higher in the roadside group
					Morphine	No significant difference
					Amphetamine	Higher amphetamine concentrations were observed in injured drivers; however, there were limited cases in the roadside survey
Cox et al. (2012) [9]	United States, Open-labeled, cross-over	Investigate whether methylphenidate delivered through a long-acting transdermal system (MTS) would reduce collision rates of young adult drivers with attention-deficit/hyperactivity disorder (ADHD)	6 month trial: 3 months no medication, 3 months MTS (random start order). MTS dose based on titration, lowest dose to achieve max symptom relief. At baseline and after condition, participants completed Cox Assessment of Risky Driving Scale. Drivers were monitored using the DriveCam recording system, and crash data.	n=17 adults (mean age [SD] 20.82 [2.40] years), 14 men, 13 white, all with a collision/citation in past 2 years	Methylphenidate, varying dosages (10-30 mg)	Long-acting methylphenidate improves self-reported risky driving in young adults with ADHD; crash risk was also reduced

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Dubois et al. (2010) [10]	Canada, Case-control study	Examine the impact of opioid analgesics on drivers involved in fatal crashes based on data from the Fatality Analysis Reporting System	Examine FARS variables related to age, sex, and drug test results (blood or urine). All medications captured in FARS were classified as either opioid positive or negative. Cases were drivers with one or more unsafe driver actions (UDAs), while controls were drivers who had no UDAs. Calculated adjusted odds ratios[8] (ORs) of any UDA by medication exposure after controlling for age, sex, other medications, and driving record.	n=72,026 passenger vehicle drivers involved in fatal crashes who tested negative for alcohol but positive for drugs; from entire sample (larger than this subset) mean age was 46 and 2/3 were male	Opioid analgesics	Results suggest that opioids negatively affect safe driving; based on findings from drivers with a confirmed BAC of zero
Gibson et al. (2009) [11]	UK, Case-crossover and case-series analyses	Investigate the impact of using various drugs on the risk of motor vehicle crashes	Case-crossover: At-risk period = 4-weeks prior to crash. 5 successive 4-week periods were used starting prior to at-risk period. Exposure was defined by prescription. Case-series: Records were grouped according to the interval between prescriptions. Outcome of interest was the first crash. Available follow-up time was	n=7,300 individuals, 18-74 with at least one crash a year, data from The Health Improvement Network, prospectively collected primary care records with	Dihydrocodeine (dosages vary/not specified) Codeine phosphate (dosages vary/not specified) Morphine (dosages vary/not specified)	Risk of motor vehicle crash is increased by the use of opioids for the duration of their usage, the risk decreasing once the medication is discontinued; the initiation of opioid treatment was associated with an increased risk of motor vehicle crash that persisted throughout the remainder of treatment but was not observed after withdrawal of treatment

[8] Adjusted odds ratios take into account other variables which may affect the outcome, such as age or gender. The odds ratio (sometimes called the crude odds) is adjusted to take into account these other variables which may impact the relationship.

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
			classified based on exposure and whether changes in risk of crash are short-lived, develop over time, or are constant.	prescription information from 255 general practices	Opioids (all)	
Gjerde et al. (2011) [12]	Norway, Case-control study	To compare the prevalence of drugs in samples from drivers killed in south-eastern Norway with random drivers and to calculate odds ratios for fatally injured drivers	Blood samples from drivers in a fatal road traffic accident were compared to a random sampling of drivers in southeast Norway.	n=204 (fatally injured drivers); controls n=10,540 non-injured drivers	Medical opioids (including Codeine, Morphine, and Methadone) Codeine (above 10 ng/ml)	Use of a single medicinal drug in isolation of other drugs/alcohol does not dramatically increase the rate of being in a fatal accident; however, opioid use is associated with higher risk (although this may occur concurrently with other drugs and alcohol)
Gomes et al. (2013) [13]	Canada, Nested case-control	Characterize the relationship between opioid dose and risk of road trauma	Case and control information was retrieved via prescription drug registries and incidence of road trauma was determined from National Ambulatory Care Reporting System. Patients were separated by opioid dose level.	n=10,600 (all prescribed opioids; cases experienced road trauma, matched controls did not), mean age=45.8, male=51.4%; sub analysis of drivers only, n=2,428 cases + n=2,428 controls	Codeine, Morphine sulfate, Oxycodone or Hydromorphone Hydrochloride, and transdermal Fentanyl patches (all drugs were converted into morphine equivalent (MEQ))	Amongst drivers there was an increased risk of road trauma correlated to increase opiate dose compared with patients prescribed very low opioid doses

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Meuleners et al. (2011) [14]	Australia, Retrospective case-crossover study	Determine the association between psychoactive medications and crash risk in drivers aged 60 and older	De-identified data from the Hospital Morbidity Data System (HMDS) were obtained for all hospital admissions from 2002-2008 of individuals aged 60 and older involved in a motor vehicle crash.	n=284 (aged 60 and older hospitalized as the result of a motor vehicle crash and prescribed opioid analgesics), male=44.7%	Opioid analgesics	Opioid usage was associated with greater risk of a motor vehicle crash requiring hospitalization in older drivers, especially in female drivers
Orriols et al. (2010) [15]	France, Registry cohort	Investigate the association between prescription medicines and the risk of road traffic crashes	Researchers determined driver responsibility and then compared responsible drivers with non-responsible drivers involved in an accident.	n=72,685 (68.5% male)	Analgesics (included opioids, other analgesics and antipyretics, and anti-migraine medication; vast majority were opioids)	No significant correlation between analgesic usage and responsibility for a roadside accident
Ravera & De Gier (2010) [16]	Netherlands, Case-control study	Assess the association between traffic accident risk and psychotropic medication exposure	Records from three separate databases (pharmacy records, traffic accident records, and driver's license records) were linked. For each accident four controls without accidents were linked based on demographic information. Researchers compared the prevalence of opioids between the two groups.	n=4,784 cases (had a traffic accident between 2000 and 2007); n=19,136 controls (adults who had a driving license and had no traffic accident during the study period)	Opioids (all drugs combined)	Drivers taking opioids were not at a higher risk of being in an accident

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Reguly et al. (2013) [17]	Canada, Case-control study	Examine the role of opioid analgesic use in male CMV truck drivers involved in fatal crashes	Driver records were used to identify CMV Drivers that used opioid analgesics and these drivers were compared with non-opioid using drivers in terms of unsafe driver actions.	n=65,867 CMV driver records; n=8,325 drug tested drivers with BAC at zero (all male over 20); n=102 drivers testing positive for opioids (age=45.5)	Opioid analgesics (Morphine (18.6%), Hydrocodone (17.6%), Methadone (12.7%), Codeine (11.8%), and Propoxyphene (10.8%))	The presence of opioid analgesics is associated with greater odds of committing an unsafe driver action among CMV drivers

Table 9: Detailed Findings for Original Articles that Address Q1a

Author (Year)	Drug(s)	Findings
Bachs et al. (2009) [1]	Codeine	1. Risk (SIR) for traffic accidents after exposure to codeine: 1.9 (CI: 1.6-2.2); Co-prescription excluded: 1.3 (CI: 1.0-1.6) 2. Risk (SIR) for males being involved in traffic accidents after exposure to codeine: 2.0 (CI: 1.6-2.4); Co-prescription excluded: 1.3 (CI: 0.9-1.7) 3. Risk (SIR) for females being involved in traffic accidents after exposure to codeine: 1.8 (CI: 1.4-2.3); Co-prescription excluded: 1.3 (CI: 0.9-1.8) 4. Risk (SIR) for traffic accidents after exposure to codeine (codeine high consumers): 2.9 (CI: 2.3-3.6); Co-prescription excluded: 0.9 (CI: 0.5-1.3) 5. Risk (SIR) for traffic accidents after exposure to codeine (males 35-54): 2.5 (CI: 1.9-3.2); Co-prescription excluded: 1.5 (CI: 1.0-2.1) 6. Risk (SIR) for traffic accidents after exposure to codeine (females 35-54): 2.0 (CI: 1.4-2.6); Co-prescription excluded: 1.7 (CI: 1.0-2.4) 7. Risk (SIR) was not increased for non-regular users (no previous use past 180 days); codeine use only increased SIR when co-prescriptions were included 8. Risk (SIR) for traffic accidents after exposure to codeine (non-regular users): 1.1 (CI: 0.7-1.5)
Bramness et al. (2012) [2]	Methadone	1. Risk (SIR) for traffic accidents after exposure to methadone: 2.1 (CI: 1.4-3.1) 2. Risk (SIR) for traffic accidents after exposure to methadone (removing all exposed to benzodiazepines during observation period): 3.4 (CI: 1.9-5.5) 3. Risk (SIR) for males being involved in traffic accidents after exposure to methadone: 2.4 (CI: 1.5-3.6) 4. Risk (SIR) for males being involved in traffic accidents after exposure to methadone (removing all exposed to benzodiazepines during observation period): 4.0 (CI: 2.2-6.6) 5. Risk (SIR) for females being involved in traffic accidents after exposure to methadone: 1.1 (CI: 0.2-3.1) 6. Risk (SIR) for females being involved in traffic accidents after exposure to methadone (removing all exposed to benzodiazepines during observation period): 1.0 (CI: 0.0-5.8)
Engeland et al. (2007) [3]	Natural opium alkaloids	1. Risk (SIR) for traffic accidents after exposure to natural opium alkaloids (within 7 days of the dispensing date): 2.0 (CI: 1.7-2.4) 2. Risk (SIR) for males being involved in traffic accidents after exposure to natural opium alkaloids (within 7 days of the dispensing date): 2.0 (CI: 1.5-2.5) 3. Risk (SIR) for males being involved in traffic accidents after exposure to natural opium alkaloids (within period of defined daily dose): 2.1 (CI: 1.8-2.4) 4. Risk (SIR) for females being involved in traffic accidents after exposure to natural opium alkaloids (within 7 days of the dispensing date): 2.0 (CI: 1.5-2.6) 5. Risk (SIR) for females being involved in traffic accidents after exposure to natural opium alkaloids (within period of defined daily dose): 1.8 (CI: 1.4-2.2)

Author (Year)	Drug(s)	Findings
Bernhoft et al. (2012) [4]	Medicinal opioids	1. Risk (odds ratio) for drivers being seriously injured while taking medicinal opioids: 7.99 (CI: 5.73-11.15); adjusted=7.37 (CI: 4.99-10.88) 2. Risk (odds ratio) for drivers being killed while taking medicinal opioid: 4.82 (CI: 2.61-8.88); adjusted=4.07 (CI: 2.14-7.72)
	Amphetamines	1. Risk (odds ratio) for drivers being seriously injured while taking amphetamines: 9.66 (CI: 4.80-19.46); adjusted=14.15 (CI: 5.82-34.42) 2. Risk (odds ratio) for drivers being killed while taking amphetamines: 25.44 (CI: 10.81-59.90); adjusted=34.34 (CI: 13.18-89.49)
Hels et al. (2013) [5]	Medicinal opioids	1. Risk (odds ratio) for drivers being seriously injured while taking medicinal opioids: 8.00 (CI: 5.73-11.18); adjusted=7.37 (CI: 4.99-10.88) 2. Odds ratio men: women 0.662 (CI: 0.59-0.74)
	Amphetamines	1. Risk (odds ratio) for drivers being seriously injured while taking amphetamines: 9.65 (CI: 4.63-20.11); adjusted=14.15 (CI: 5.82-34.42) 2. Odds ratio men: women 0.652 (CI: 0.58-0.74)
Hels et al. (2012) [6]	Medicinal opioids	1. Adjusted odds ratio for getting seriously injured while positive for opioids (all countries): 9.06 (CI: 6.40-12.83) 2. Adjusted odds ratio for getting seriously injured while positive for opioids in Belgium: 4.33 (CI: 1.58-11.59) 3. Adjusted odds ratio for getting seriously injured while positive for opioids in Denmark: 5.72 (CI: 3.06-10.61) 4. Adjusted odds ratio for getting seriously injured while positive for opioids in Finland: 5.40 (CI: 0.68-42.97) 5. Adjusted odds ratio for getting seriously injured while positive for opioids in Italy: 11.16 (CI: 3.38-36.88) 6. Adjusted odds ratio for getting seriously injured while positive for opioids in Lithuania: n.a. 7. Adjusted odds ratio for getting seriously injured while positive for opioids in Netherlands: 5.96 (CI: 0.73-48.84) 8. Adjusted odds ratio for getting seriously injured while positive for opioids male vs. female: 0.83 (CI: 0.60-1.14)
	Amphetamines	1. Adjusted odds ratio for getting seriously injured while positive for amphetamines (all countries): 8.35 (CI: 3.91-17.83) 2. Adjusted odds ratio for getting seriously injured while positive for amphetamines in Belgium: n.a 3. Adjusted odds ratio for getting seriously injured while positive for amphetamines in Denmark: 49.94 (CI: 2.80-891.67) 4. Adjusted odds ratio for getting seriously injured while positive for amphetamines in Finland: n.a 5. Adjusted odds ratio for getting seriously injured while positive for amphetamines in Italy: n.a 6. Adjusted odds ratio for getting seriously injured while positive for amphetamines in Lithuania: 0.50 (CI: 0.04-6.88) 7. Adjusted odds ratio for getting seriously injured while positive for amphetamines in Netherlands: 8.87 (CI: 1.84-42.86) 8. Adjusted odds ratio for getting seriously injured while positive for amphetamines male vs. female: 0.82 (CI: 0.59-1.14)
	Medicinal opioids	1. Adjusted odds ratio for getting killed while positive for opioids (all countries): 4.82 (CI: 2.60-8.93) 2. Adjusted odds ratio for getting killed while positive for opioids in Finland: 3.82 (CI: 1.60-9.16) 3. Adjusted odds ratio for getting killed while positive for opioids in Norway: 5.64 (CI: 0.73-43.82) 4. Adjusted odds ratio for getting killed while positive for opioids in Portugal: 8.93 (CI: 1.52-52.45) 5. Adjusted odds ratio for getting killed while positive for opioids in Sweden: 2.85 (CI: 0.68-12.03) 6. Adjusted odds ratio for getting killed while positive for opioids male vs. female: 1.59 (CI: 1.20-2.12)

Author (Year)	Drug(s)	Findings
	Amphetamines	1. Adjusted odds ratio for getting killed while positive for amphetamines (all countries): 24.09 (CI: 9.72-59.71) 2. Adjusted odds ratio for getting killed while positive for amphetamines in Finland: 18.39 (CI: 2.83-119.72) 3. Adjusted odds ratio for getting killed while positive for amphetamines in Norway: 22.99 (CI: 4.12-128.44) 4. Adjusted odds ratio for getting killed while positive for amphetamines in Portugal: n.a. 5. Adjusted odds ratio for getting killed while positive for amphetamines in Sweden: 63.65 (CI: 15.16-267.27) 6. Adjusted odds ratio for getting killed while positive for amphetamines male vs. female: 1.58 (CI: 1.18-2.10)
Kuypers et al. (2012) [7]	Medicinal opioids	1. Adjusted odds ratio for having an accident while positive for medicinal opiates: 2.91 (0.97–8.68) 2. Crude odds ratio for having an accident while positive for medicinal opioids: 3.42 (1.27–9.21)
	Amphetamines	1. Adjusted odds ratio for having an accident while positive for amphetamines: n.a. 2. Crude odds ratio for having an accident while positive for amphetamines: 54.82 (6.09–493.12)
Van der Linden et al. (2013) [8]	Codeine	1. Mann Whit-ney test for difference between injured drivers/roadside drivers testing positive for codeine: -1.12 (n.s.)
	Methadone	1. Mann Whit-ney test for difference between injured drivers/roadside drivers testing positive for methadone: -1.94 (p=0.053)
	Morphine	1. Mann Whit-ney test for difference between injured drivers/roadside drivers testing positive for morphine: 0.10 (n.s.)
	Amphetamine	1. Mann Whit-ney test for difference between injured drivers/roadside drivers testing positive for amphetamine: 2.09 (p=0.037)
Cox et al. (2012) [9]	Methylphenidate	1. CARDS total score of self-reported risky driving behaviors (medication/no medication): t = -1.684, p = 0.059 2. Comparison of erratic driving events (medicated/not medicated): n=1,589/n=1,570, t=0.11, ns 3. Comparison of collisions (medication/no medication): n=0/n=8, z= 2.83, p<0.005
Dubois et al. (2010) [10]	Opioid analgesics	1. Risk (adjusted odds ratio) for female drivers of performing an unsafe driving action while taking opioid analgesics from ages 25 (OR: 1.35; CI: 1.05-1.74) to 55 (OR: 1.30; CI: 1.07-1.58); increased by 30–42% for females aged 25–55 (no increase for women 56+) 2. Risk (adjusted odds ratio) for male drivers of performing an unsafe driving action while taking opioid analgesics from ages 25 (OR: 1.66; CI: 1.32-2.09) to 65 (OR: 1.39; CI: 1.17-1.67); increased by 40–74% for male drivers aged 25–65 (no increase for men aged 66+)
Gibson et al. (2009) [11]	Dihydrocodeine	1. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking dihydrocodeine (4 week period up to and including the date of the prescription): 11.73 (99% CI: 10.21-13.49) 2. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking dihydrocodeine (4-week period following the first prescription of a course of treatment): 1.60 (99% CI: 1.14-2.25) 3. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking dihydrocodeine (remainder of exposed time): 1.05 (99% CI: 0.78-1.42) 4. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking dihydrocodeine (12-week period following the end of exposure): 1.15 (99% CI: 0.91-1.47) 5. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking dihydrocodeine (second 12-week period following the end of exposure): 1.03 (99% CI: 0.79-1.35)

Author (Year)	Drug(s)	Findings
	Codeine phosphate	1. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking codeine phosphate (4 week period up to and including the date of the prescription): 10.90 (99% CI: 9.33-12.74) 2. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking codeine phosphate (4-week period following the first prescription of a course of treatment): 1.61 (99% CI: 1.11-2.32) 3. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking codeine phosphate (remainder of exposed time): 1.33 (99% CI: 0.88-2.00) 4. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking codeine phosphate (12-week period following the end of exposure): 0.93 (99% CI: 0.69-1.24) 5. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking codeine phosphate (second 12-week period following the end of exposure): 0.85 (99% CI: 0.62-1.18)
	Morphine	1. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking morphine (4 week period up to and including the date of the prescription): 3.14 (99% CI: 1.60-6.15) 2. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking morphine (4-week period following the first prescription of a course of treatment): 1.16 (99% CI: 0.39-3.45) 3. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking morphine (remainder of exposed time): 0.87 (99% CI: 0.43-1.75) 4. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking morphine (12-week period following the end of exposure): 1.10 (99% CI: 0.49-2.47) 5. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking morphine (second 12-week period following the end of exposure): 1.42 (99% CI: 0.63-3.16)
	Opioids (all)	1. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking opioids (4 week period up to and including the date of the prescription): 10.90 (99% CI: 9.96-11.93) 2. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking opioids (4-week period following the first prescription of a course of treatment): 1.70 (99% CI: 1.39-2.08) 3. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking opioids (remainder of exposed time): 1.29 (99% CI: 1.08-1.54) 4. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking opioids (12-week period following the end of exposure): 1.02 (99% CI: 0.87-1.20) 5. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking opioids (second 12-week period following the end of exposure): 0.90 (99% CI: 0.75-1.08)

Author (Year)	Drug(s)	Findings
	Opioids (all)	1. Risk (odds ratio) for being involved in a motor vehicle crash while taking opioids (29-56 days before motor vehicle crash): 1.22 (99% CI: 0.94-1.59) 2. Risk (odds ratio) for being involved in a motor vehicle crash while taking opioids (57-84 days before motor vehicle crash): 1.46 (99% CI: 1.12-1.91) 3. Risk (odds ratio) for being involved in a motor vehicle crash while taking opioids (85-112 days before motor vehicle crash): 1.25 (99% CI: 0.97-1.62) 4. Risk (odds ratio) for being involved in a motor vehicle crash while taking opioids (113-140 days before motor vehicle crash): 1.45 (99% CI: 1.11-1.90) 5. Risk (odds ratio) for being involved in a motor vehicle crash while taking opioids (141-168 days before motor vehicle crash): 1.44 (99% CI: 1.11-1.85)
Gjerde et al. (2011) [12]	Medical opioids	1. Risk (odds ratio) for drivers being fatally injured in a motor vehicle accident while taking medicinal opioids: 4.1 (CI: 1.5-11.5); adjusted= 5.7 (CI: 2.0-16.2)
	Codeine	1. Risk (odds ratio) for drivers being fatally injured in a motor vehicle accident while taking codeine: 2.3 (CI: 0.5-9.4); adjusted= 3.0 (CI: 0.7-12.6)
Gomes et al. (2013) [13]	Codeine, Morphine sulfate, Oxycodone or Hydromorphone Hydrochloride, and transdermal Fentanyl patches	1. Risk (adjusted odds ratio) of road trauma among drivers taking low opioid doses (20-49 MEQ) compared to very low opioid doses (< 20 MEQ): 1.21 (CI: 1.02-1.42) 2. Risk (adjusted odds ratio) of road trauma among drivers taking moderate opioid doses (50-99 MEQ) compared to very low opioid doses (< 20 MEQ): 1.29 (CI: 1.06-1.57) 3. Risk (adjusted odds ratio) of road trauma among drivers taking high opioid doses (100-199 MEQ) compared to very low opioid doses (<20 MEQ): 1.42 (CI: 1.15-1.76) 4. Risk (adjusted odds ratio) of road trauma among drivers taking very high opioid doses (≥ 200 MEQ) compared to very low opioid doses (< 20 MEQ): 1.23 (CI: 1.02-1.49)
Meuleners et al. (2011) [14]	Opioid analgesics	1. Risk (odds ratio) for a crash involving hospitalization for older drivers (aged ≥ 60 years) prescribed opioid analgesics: 1.5 (CI: 1.0–2.3) 2. Risk (odds ratio) for a crash involving hospitalization for female older drivers (aged ≥ 60 years) prescribed opioid analgesics: 1.8 (CI: 1.1–3.0) 3. Risk (odds ratio) for a crash involving hospitalization for male older drivers (aged ≥ 60 years) prescribed opioid analgesics: 1.2 (CI: 0.6–2.4)
Orriols et al. (2010) [15]	Analgesics	1. Risk (odds ratio) for a driver being responsible for an automobile crash while taking analgesics: 1.04 (CI: 0.94-1.15)
Ravera & De Gier (2010) [16]	Opioids	1. Risk (odds ratio) for drivers being in a road traffic accident while taking opioids: 1.17 (CI: 0.74-1.85) 2. Risk (odds ratio) for drivers being in road traffic accidents while taking opioids: females (1.27; CI: 0.63-2.55); males (1.10; CI: 0.60-2.01) 3. Risk (odds ratio) for being in a road traffic accident while taking opioids: aged < 30 years (1.93; CI: 0.38-9.96); aged 30-60 years (1.48; CI: 0.88-2.48); aged > 60 years (0.35; CI: 0.08-1.45)

Author (Year)	Drug(s)	Findings
Reguly et al. (2013) [17]	Opioid analgesics	1. Risk (odds ratio) for male truck drivers of committing at least one unsafe driving action while testing positive for opioid analgesics: 1.83 (CI: 1.23-2.10); adjusted OR: 2.80 (CI: 1.64-1.81) 2. Risk (odds ratio) for 35-yr-old male truck drivers of committing at least one unsafe driving action while testing positive for opioid analgesics: 1.46 (CI: 0.82-2.59) 3. Risk (odds ratio) for 45-yr-old male truck drivers of committing at least one unsafe driving action while testing positive for opioid analgesics: 2.80 (CI: 1.64-4.81) 4. Risk (odds ratio) for 55-yr-old male truck drivers of committing at least one unsafe driving action while testing positive for opioid analgesics: 2.19 (CI: 1.24-3.87) 5. Risk (odds ratio) for 65-yr-old male truck drivers of committing at least one unsafe driving action while testing positive for opioid analgesics: 0.70 (CI: 0.25-1.98)

Systematic literature reviews that address Q1a are shown in the Table 10 below.

Table 10: Systematic Literature Reviews that Address Q1a

Author (Year)	Study Objective	Databases Searched	Drug(s) (Dose)	Findings and Conclusions
Dassanayake et al. (2011) [18]	Examine the association of opioids with the risk of traffic accidents	PubMed and EMBASE (1966-2010)	Opioids (various)	**Conclusions:** Opioid users may be at a higher risk of traffic accidents; however, experimental evidence on their effects on driving is scarce. **Findings:** Limited findings based on 5 studies
ECRI & MANILA (2006) [19]	Investigate the relationship between licit use of Schedule II drugs and CMV crashes	Medline, PubMed (pre-Medline), EMBASE, PsycINFO, CINAHL, TRIS, and the Cochrane library (thru 2006)	Opioids (various)	**Conclusions:** No data to address the link between licit use and crash risk. **Findings:** Did not find any data to address this relationship
			Stimulants	**Conclusions:** No data to address the link between licit use and crash risk. **Findings:** Did not find any data to address this relationship

Author (Year)	Study Objective	Databases Searched	Drug(s) (Dose)	Findings and Conclusions
Fishbain et al. (2003) [20]	To determine what evidence, if any, exists for or against opioid-related driving skill impairment in opioid-dependent/tolerant patients	Medline, Psychological Abstracts, Science Citation Index, and the National Library of Medicine Physician Data Query (PDQ) (1966-2001)	Opioids (various)	**Conclusions:** No evidence for higher accident risk. **Findings:** Strong, consistent evidence for no greater incidence of motor vehicle violations/motor vehicle accidents versus comparable controls of opioid-maintained patients
Monárrez-Espino et al. (2013) [21]	To assess the epidemiological evidence associating the use of analgesics with the occurrence of road traffic crashes in senior drivers, including a meta-analysis with specific focus on opioids	PubMed, EMBASE, SCOPUS, Science Direct, Google Scholar (1991-2012)	Opioids (various)	**Conclusions:** Mixture of significant and non-significant results including differences across estimates between and within studies. **Findings:** 1. Marginally positive pooled estimates computed in the meta-analyses: Model I: OR 1.20; CI: 1.08–1.33; Model II: OR: 1.37; CI: 1.04–1.82 2. Review of relevant studies show mixed results, with nearly half showing positive findings
Orriols et al. (2009) [22]	Investigate effects of medicinal drugs on traffic safety	Medline (1979-2008)	Opioids	**Conclusions:** Studies on opioids showed mixed results; some found effects and some did not. **Findings:** A majority of relevant studies show increased risk, but no significant association between risk of road traffic accidents and opioid use; however this may be due to not enough power in several studies

Author (Year)	Study Objective	Databases Searched	Drug(s) (Dose)	Findings and Conclusions
Raes et al. (2008) [23]	Investigate evidence from experimental and field studies of the relationship between drug use, driving impairment, and traffic accidents	ISI Web of Science, PubMed (Medline), Psychinfo and Transport (not provided)	Opioids	**Conclusions:** Limited studies demonstrate inconclusive evidence on accident risk associated with opiate use. Meta-analysis shows elevated accident risks. **Findings:** 1. Drivers under the influence of opiates alone are at increased risk of being involved in an accident, as indicated by meta-analysis: RR=3.2 (CI: 1.4–6.9) and OR=3.7 (CI: 1.4–10.0) 2. Review of relevant studies found that a majority show increased risk of traffic accidents while taking opioids 3. Two out of three responsibility analyses found no increased risk of being responsible for an accident, whereas the third found an increased risk
			Amphetamines	**Conclusions:** Limited studies tend not to show an effect. **Findings:** 1. One (of four) studies found association with an increased risk of involvement in an accident 2. No significant increased risk of being responsible for an accident was found in responsibility studies
Strand et al. (2013) [24]	Review treatment with methadone related to traffic accident risk	MEDLINE, EMBASE, and PsycINFO (thru 2010)	Methadone (2-400 mg)	**Conclusions:** Recent studies have found an increased risk of traffic accident for methadone-maintained patients. **Findings:** Two recent and large studies found an increased risk of traffic accident involvement and an increased risk of being responsible for an accident when exposed to methadone

Author (Year)	Study Objective	Databases Searched	Drug(s) (Dose)	Findings and Conclusions
Wilhelmi & Cohen (2012) [25]	Investigate whether opioid-stabilized patients are more likely to have motor vehicle accidents	PubMed (not provided)	Morphine (30-60 mg); Hydrocodone/Acetaminophen (50-20 mg/500-1000 mg); Oxycodone (10-30 mg); Acetaminophen (1000 mg)	**Conclusions:** Review of relevant studies found that a majority show no difference in motor vehicle accidents or motor vehicle violations for stable use opioid patients. **Findings:** Seven of eight studies found no increase in the number of motor vehicle violations or motor vehicle accidents compared with age-matched controls

Findings

Findings are presented for opioids as a group (where the effects of individual drugs were not separately reported) as well as for codeine, morphine, natural opium alkaloids, and methadone. For stimulants, findings are presented for amphetamines and for methylphenidate. In each section, results are first reported for original research studies, and then for any pertinent systematic reviews. Several of the original research studies share a common data collection effort. Findings are co-reported for shared data sets.

Opioids

Twelve original research studies investigated the risk between opioids and crash risk. These studies investigated the link between opioid use and various outcomes, including driver fatalities, driver injuries, crash risk, and unsafe driver actions.

Three of these studies (Bernhoft et al. [4], Hels et al. [6], and Gjerde et al. [12]) investigated the link between opioids and drivers getting killed, although two of them (Bernhoft et al. [4] and Hels et al. [6]) share a common dataset. All found a significantly increased adjusted odds ratio (which takes into account other variables which may have affected the outcome) for driver fatalities (adjusted OR=4.07 (CI: 2.14-7.72); adjusted OR=4.82 (CI: 2.60-8.93); adjusted OR= 5.7 (CI: 2.0-16.2)).

Three studies using the same data collection effort investigated the endpoint of the driver becoming seriously injured (Bernhoft et al. [4], Hels et al. [5], and Hels et al. [6]). All three found an elevated and significant adjusted odds ratio for serious driver injury, with two reporting identical findings (adjusted=7.37 (CI: 4.99-10.88); adjusted=7.37 (CI: 4.99-10.88); adjusted=9.06 (CI: 6.40-12.83)). The Hels et al. [6] study calculated the odds across all reporting countries as well as individual countries. Adjusted odds were significantly increased overall and for three countries, and were elevated but not significantly increased in two other countries with wide confidence intervals. Two additional studies investigated related questions. Gomes et al. (2013) [13] looked at adjusted odds for road trauma for drivers taking very low doses of opioids (<20 morphine equivalent, MEQ) to those taking higher doses (20-49 MEQ, 50-99 MEQ, 100-199 MEQ, and 200+ MEQ). They found elevated odds for all comparisons, with the highest risk for drivers taking 100-199 MEQ (adjusted odds=1.42 (CI: 1.15-1.76)). Meuleners et al. [14] investigated the odds of a crash involving hospitalization for older drivers (>60 years old). The odds were elevated only for female drivers (adjusted OR=1.8 (CI: 1.1–3.0)).

Three studies investigated the association between opioid use and crash risk (Kuypers et al. [7], Gibson et al. [11], and Ravera & De Gier [16]). Kuypers et al. [7] found an elevated risk using crude but not adjusted odds (crude OR=3.42 (1.27–9.21) and adjusted OR=2.91 (0.97–8.68)). Gibson et al. [11] found an elevated incident rate ratio beginning with the time prior to and including the fulfilling of a prescription (IRR=10.90 (99% CI: 9.96-11.93)), and continuing four weeks after the prescription was filled (IRR=1.70 (99% CI: 1.39-2.08)) which remained elevated through the remainder of the exposed time (IRR=1.29 (99% CI: 1.08-1.54)). Ravera & De Gier [16] did not find a significant increase in the odds of being in an accident (odds=1.17 (CI: 0.74-1.85)). Orriols et al. [15] investigated the related question of whether drivers taking analgesics are more likely to be declared responsible for an accident: they did not find an elevated risk (odds ratio=1.04 (CI: 0.94-1.15)).

Finally, two studies looked at the risk of unsafe driver actions for drivers taking opioids (Dubois et al. [10] and Reguly et al. [17]). Dubois et al. [10] found the risk was elevated by 30-42% for females aged 25-55 and by 40-74% for males aged 25-65. Reguly et al. [17] looked specifically at CMV drivers and found the adjusted odds of committing at least one unsafe driver action while taking opioids was elevated (adjusted OR=2.80 (CI: 1.64-1.81)). The risk was highest for a 45-year-old male driver (adjusted OR=2.80 (CI: 1.64-4.81)).

Seven systematic reviews investigated the risk of traffic accidents and injuries for drivers taking opioids. Fishbain et al. [20] found no evidence that drivers taking opioids were at greater risk of accident, although the study only examined opioid-maintained patients. Wilhelmi & Cohen [25] also found no effects in seven of eight studies reviewed, again looking at opioid-maintained patients. ECRI & MANILA [19] concluded there was insufficient data to address this topic. Dassanayake et al. [18] found limited evidence that suggests that opioid users may be at higher risk. Orriols 2009 [22] found mixed results with most studies showing increased risk, but no significant association, possibly due to low power. Monárrez-Espino et al. [21] and Raes et al. [23] conducted meta-analyses, both of which showed elevated risk. Monárrez-Espino et al. [21] conducted two models, both of which showed increased risk (Model I: OR=1.20 (CI: 1.08–1.33); Model II: OR=1.37 (CI: 1.04–1.82)). Raes et al. [23] found increased odds of being in an accident (OR=3.7 (CI: 1.4–10.0)).

Codeine

Four studies investigated the relationship between codeine exposure and traffic accident risk. In a large cohort study using national registry data for prescription drugs and automobile crashes, Bachs et al. [1] found an increased risk for traffic accidents after exposure to codeine (SIR=1.9 (CI: 1.6-2.2)). However, the risk decreased and was no

longer significant when co-prescriptions were excluded (SIR=1.3 (CI: 1.0-1.6)). In another large study using crash data and prescription records from primary physicians, Gibson [11] found an increased incident rate ratio (IRR) for involvement in a motor vehicle crash when starting a prescription for codeine phosphate (IRR=10.90 (99% CI: 9.33-12.74)) and for four weeks after starting a prescription (IRR=1.61 (99% CI: 1.11-2.32)). Likewise, the risk for dihydrocodeine was elevated at the time the prescription started (IRR=11.73 (99% CI: 10.21-13.49)) and for four weeks from the date of the prescription (IRR=1.60 (99% CI: 1.14-2.25)). However, Van der Linden et al. [8] did not find a difference in a test of injured drivers and roadside controls. Likewise, Gjerde et al. [12] found in a case controlled study comparing fatally injured drivers to roadside controls that there was not an increased risk for being fatally injured in a motor vehicle accident while taking codeine, although the confidence interval on this finding was quite large (adjusted OR: 3.0 (CI: 0.7-12.6)).

Morphine

Only one study looked specifically at morphine. Van der Linden et al. [8] found no difference between morphine levels for injured drivers and roadside controls.

Natural Opium Alkaloids

Only one study provided data on natural opium alkaloids. In a large cohort study using national registry data for prescription drugs and automobile crashes, Engeland et al. [3] found an increased risk for traffic accidents after exposure to natural opium alkaloids (SIR=2.0 (CI: 1.7-2.4)).

Methadone

Two original research studies and one systematic review addressed the topic of methadone and accident risk. In a large cohort study using national registry data for prescription drugs and automobile crashes, Bramness et al. [2] found an increased risk for traffic accidents after exposure to methadone (SIR=2.1 (CI: 1.4-3.1)). The elevated risk remained and increased after removing all participants exposed to benzodiazepines during the observation period and was higher for males (SIR=4.0 (CI: 2.2-6.6)). However, Van der Linden et al. [8] found an opposing result, with a trend toward roadside controls having greater exposure to methadone than injured drivers. The identified systematic review (Strand et al. [24]) found that while earlier studies had shown mixed or no results, recent studies (including the Bramness study and one other) have been inclined to find an increased risk of traffic accident involvement and an increased risk of being responsible for an accident when exposed to methadone.

Amphetamines

Five original research studies reported on the effects of amphetamines, however they all shared the same data collection. The adjusted odds ratio for being seriously injured while driving taking amphetamines was reported in both Bernhoft et al. [4] and Hels et

al. [5] as 14.15 (CI: 5.82-34.42) while Hels et al. [6] reported it as 8.35 (CI: 3.91-17.83). Hels et al. [6] also reported adjusted odds of being seriously injured for four separate countries, two of which were significantly higher. The odds of the driver being killed were reported in Bernhoft et al. [4] as 34.34 (CI: 13.18-89.49) while Hels et al. [6] reported it as 24.09 (CI: 9.72-59.71). Hels et al. [6] also reported adjusted odds of being killed for three separate countries, all of which were elevated. Kuypers et al. [7] reported the crude odds ratio for having an accident while positive for amphetamines as 54.82 (CI: 6.09–493.12). Finally, Van der Linden et al. [8] found a significant difference between injured drivers and roadside drivers, with more injured drivers testing positive for amphetamines ($p<0.05$).

In one systematic review, Raes et al. [23] found four relevant studies, of which only one showed impairing effects of amphetamine.

Methylphenidate

Only one study looked specifically at methylphenidate. Cox et al. [9] found that in a study of young drivers with ADHD, there was a trend suggesting that long-acting methylphenidate improved self-reported risky driving ($p=0.059$). The medicated group also had fewer collisions ($p<0.01$).

Conclusions

There is moderate evidence to support the contention that licit use of opioids increases the risk of a motor vehicle crash. Several large and recent studies link opioid use to increased risk of driver fatalities, driver injury, crash risk, and unsafe driver actions. Most identified studies show increased risk. However, many of the findings are drawn from the same large European dataset, and many of them also classify all opioids together. Results for specific opioids are more limited and less convincing.

There is weak evidence to support the contention that licit use of stimulants increases the risk of a motor vehicle crash. Most of the available evidence pertains to amphetamines and comes from a large European study which showed an increased risk of driver fatalities, driver injury, and crash risk. The use of stimulants to address driver medical conditions such as ADHD may improve driver crash risk based on one small study. Further research is required.

Research Question 1b

Question 1b asks: 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 Vigilance Tasks (PVT))?

Evidence Base for Question 1b

The evidence base for Question 1b consists of n=29 studies, as shown in Figure 3. Findings include n=20 original research articles and n=9 systematic reviews.

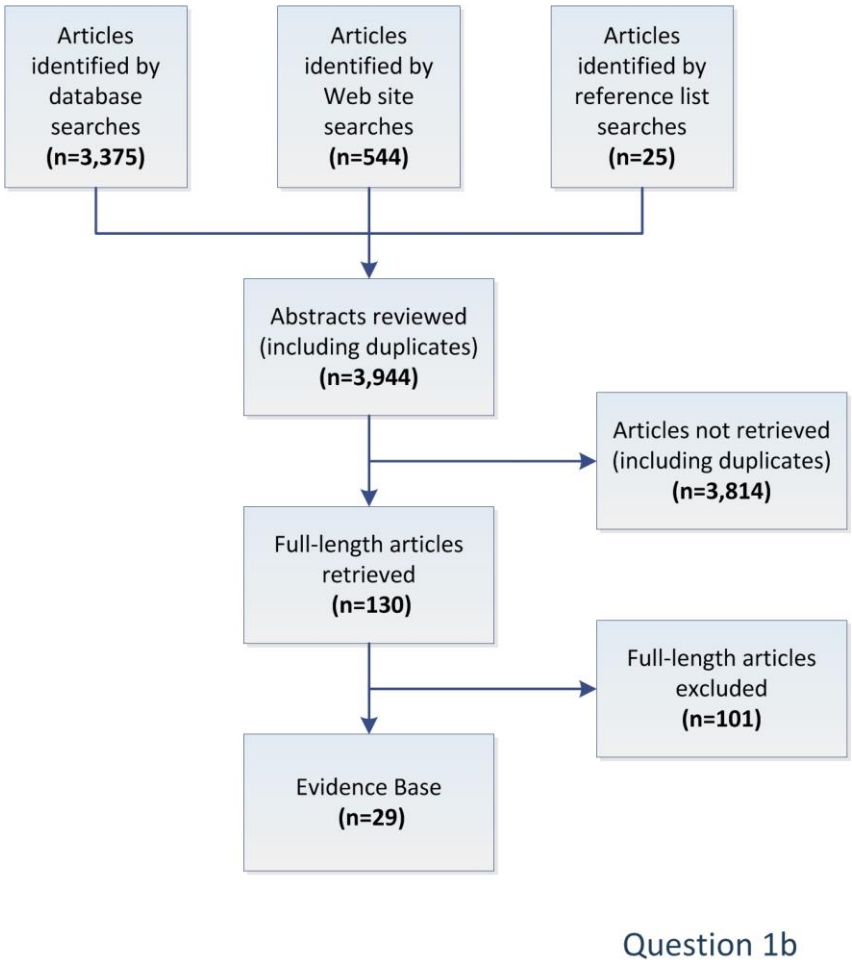
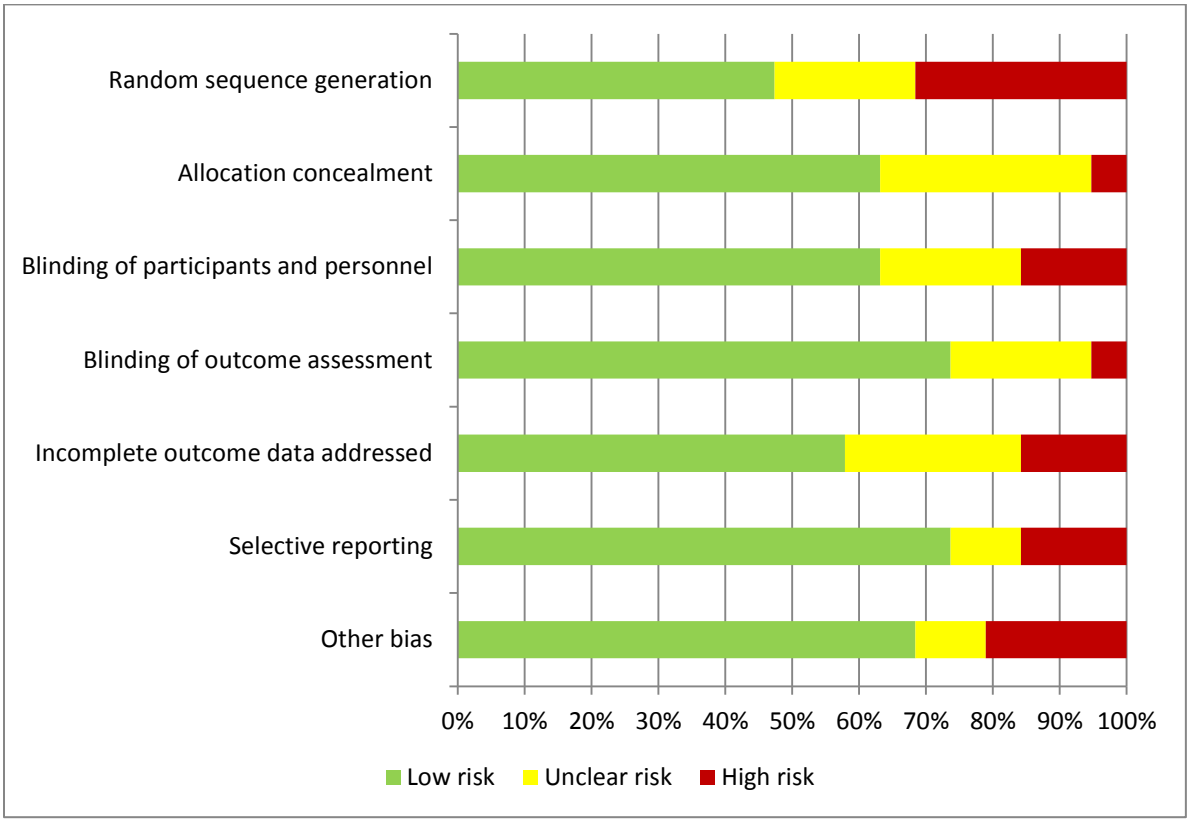


Figure 3: Evidence base, Question 1b

Quality of Included Studies

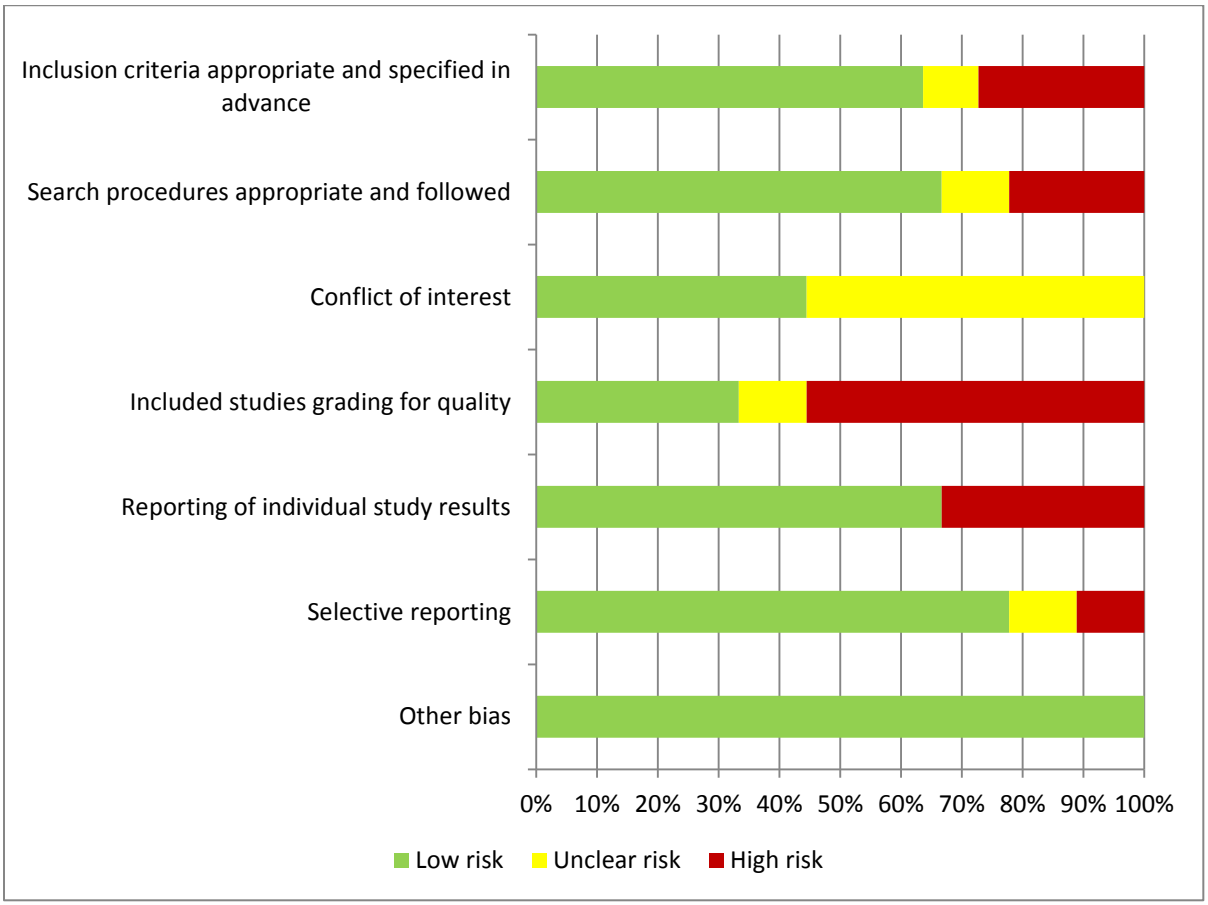
The quality ratings for the original research articles are presented in Table 11. The studies are of moderate quality.

Table 11: Study Quality for Q1b Original Research Articles



The systematic review articles are likewise of moderate quality, as shown in Table 12. Very few of them graded the included studies for quality, and some did not report all individual study results.

Table 12: Study Quality for Q1b Systematic Review Articles



Summaries of Included Studies

The original research articles that address Q1b are shown in the tables below. Table 13 shows information about the study design and conclusions for original research studies on opiates. Table 14 shows detailed findings for each of the original research articles on opiates. Table 15 shows information about the study design and conclusions for original research studies on stimulants. Table 16 shows detailed findings for each of the original research articles on stimulants. The two studies that share a common data collection effort are grouped together.

Table 13: Study Design and Conclusions for Original Articles that Address Q1b on Opiates

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Amato et al. (2013) [26]	France, Double-blind, randomized, placebo-controlled study, balanced crossover	Evaluate the dose–effect relationship of three usual therapeutic doses of codeine/paracetamol on driving ability, psychomotor performance, and subjective alertness, in link with blood concentrations, in healthy young volunteers	Each participant took part in four sessions spaced two weeks apart. They received one of three doses or placebo; serum concentration was measured at 1 and 4 hours, also completed simulated driving and other tests.	n=16 healthy volunteers (8 men) average age=22.4 years, weight=64.15 kg, and height= 171.80 cm	Codeine/paracetamol (20/400 mg, 40/800 mg, 60/1200 mg)	Found no dose effect with usual therapeutic doses of codeine/ paracetamol in a single intake and did not show impairment of driving or vigilance.

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Baewert et al. (2007) [27]	Austria, Case-control study	Evaluate driving aptitude and traffic-relevant performance at peak and trough medication levels in opioid-dependent patients receiving methadone	Patients on methadone maintenance (MM) therapy were matched to controls and subjects were compared on seven traffic psychology tests.	n=20 MM patients (7 male) (10 at peak level (1.5 hours after administration), 10 at trough level (20 hours after administration)), age = 27.9; matched controls for each subject (range: n = 3-56) same age, sex, and intelligence	Methadone (52.7 mg ± 21.6)	Patients at trough level showed some impairment compared with patients at peak level when reactive stress tolerance and visual structuring ability were measured. Methadone did not appear to affect orientation in a complex environment, observation capacity, concentration, or attentiveness.
Gaertner et al. (2006) [28]	Germany, Case-control, non-inferiority	Examine the cognitive and psychomotor effects of controlled release oxycodone in patients receiving long-term treatment; non-inferiority test to compare oxycodone use to an alcohol concentration of 0.05%	Each participant was asked to perform a battery of tests; medication usage was assessed from blood sample given before each session.	n=30 adult outpatients suffering from non-cancer pain and responsive to opioids + n=90 healthy controls	Oxycodone (controlled release), average dose=63 mg	Failed to demonstrate statistical non-inferiority of patients receiving oxycodone compared with controls (using as the delta level impairment caused by BAC=0.05). When weaker statistical analyses were performed, patients' psychomotor performance did not deviate significantly from the results of an age-independent control group. Oxycodone dose was correlated with three measures of impaired driving.

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Gruber et al. (2006) [29]	United States, Cohort study	Examine cognitive functioning in a group of opiate-dependent subjects at the beginning of a methadone maintenance (MM) program and after treatment	Subjects were administered neuropsychological measures in two sessions lasting 60-90 minutes—the first at baseline and the second after two months treatment. Tests included measures sensitive to frontal/executive functioning, verbal learning and memory, visuospatial learning and memory, attention and psychomotor speed.	n=17 (11 men), mean age= 41.2 years	Methadone (average 68.0 ± 21.7mg)	MM improved cognitive performance, particularly on tests of learning and memory. These improvements do not appear to be the result of practice effects.
Nilsen et al. (2011) [30]	Norway, Case-control study	Investigate if codeine influences driving ability in a simulator	Subjects from healthy and non-opioid using pain groups participated in two driving tests with the second test 4 hours after the first. Codeine using patients were tested during peak and trough periods roughly 1 hour after receiving codeine and 5-9 hours after receiving codeine.	n=60 (20 healthy patients, 20 patients with chronic pain not currently prescribed codeine, 20 patients with chronic pain prescribed codeine over long-term)	Codeine (median dose 180 mg)	Codeine does not impair patients with chronic pain over and above the impairment of chronic pain itself; long-lasting pain may increase reaction time and reduce the ability to respond effectively to stimuli while driving in traffic. No significant difference between chronic pain patients using and not using opioids. No significant difference between peak and trough periods for opioid patients.

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Prosser et al. (2009) [31]	United States, Case-control study	Assess the functioning of sustained attention in subjects with a history of opiate dependence using clinical measures and positron emission tomography (PET)	A test of auditory sustained attention was administered. Simultaneous measurement of regional glucose metabolism was made by flourodeoxyglucose PET. Subject groups were compared on the measures of sustained attention and regional cerebral glucose metabolism.	n=10 methadone maintained opiate-dependent patients (9 male), mean age= 40.6 [MM]. n=13 opiate dependent patients (11 male) in protracted abstinence, mean age 41.23 [PA]. n=14 healthy volunteers (10 male), mean age = 33.0 [CON]	Methadone	Subjects with a history of opiate addiction have worse performance on an auditory task than healthy subjects: fewer correct responses, greater number of errors of omission and commission, and a reduced ability to distinguish signal from noise. Subjects receiving methadone replacement therapy have worse performance than do subjects in protracted abstinence. There is increased brain activity in the healthy comparison group relative to the former opiate addicts and increased brain activity in the protracted absence group relative to the MMT group.
Schumacher et al. (2011a) [32]	Germany, Non-randomized control trial	Assess driving impairment of patients on stable opioid analgesic treatments in computerized driving tasks	Blood, saliva, and urine samples were collected. All participants completed the Vienna Test System (computer simulator) plus three additional tests to measure driver fitness skills. All participants gave self-assessments on the KSS (to measure sleepiness). Controls completed the driving tests once sober, and once two weeks later with a BAC=0.05%.	n=26 patients recruited from the pain outpatient department (58% male, mean age=54.00); n=21 healthy volunteers (62% male, mean age=43.10)	Oxycodone (10 mg/day, slow release), Oxycodone combined with Naloxone (10 mg/day, slow release), Hydromorphone (4 mg /day, slow release) or Morphine (20 mg/day, slow release), Fentanyl (12 g/h, transdermal), Buprenorphine (10g/h, transdermal) [Patients had been treated with one of these]	Patients with chronic pain treated with stable doses of opioid analgesics show impairment in driving related skills on a simulator compared to healthy controls.

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Schumacher et al. (2011b) [33]	Germany, Non-randomized control trial	Assess the risk of having a motor vehicle accident while taking prescribed medications in actual driving conditions	Blood, saliva, and urine samples were taken from all participants. Participants completed a road tracking test on a primary highway, and two weeks later a car following test. Controls completed the driving tests once sober, and once two weeks later with a BAC=0.05%.	n=39 (20 patients; 19 controls)	Oxycodone (10 mg/day, slow release), Oxycodone combined with Naloxone (10 mg/day, slow release), Hydromorphone (4 mg /day, slow release), Morphine (20 mg/day, slow release), Fentanyl (12 g/h, transdermal), or Buprenorphine (10g/h, transdermal) [Patients had been treated with one of these for at least 4 weeks]	Patients on stable doses of opioids did not differ in driving skills on a road test from sober controls.
Verster & Roth (2011) [34]	Netherlands, Double-blind placebo controlled crossover case-control study	Assess the effect of medicinal opiates using on-the-road driving tests and psychometric tests	Treatment sequences were randomized across participants. One hour after treatment, a standardized driving test was administered. Approximately 2.5 hours after intake tests were performed. Test days were separated by a washout period of seven days.	n=18	Oxycodone/Paracetamol (5/325mg) Oxycodone/Paracetamol (10/650 mg)	Relative to placebo, oxycodone/paracetamol negatively impacts tracking test and divided attention tasks.

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Zacny & Gutierrez (2011) [35]	United States, Double-blind, randomized, placebo-controlled study, balanced crossover	Assess the effects of oxycodone on psychomotor functioning	Patients took part in six sessions. Subjects were given either the placebo or 10 mg of oxycodone and asked to perform various tests.	n=14 (8 male, age=26.7, BMI (kg/m2)=23.0)	Oxycodone (10mg)	There was no evidence of impairment in the active drug conditions compared to placebo.
Zacny & Lichtor (2008) [36]	United States, Double-blind, randomized, placebo-controlled crossover study	Compare the effects of oxycodone and morphine on the same subject and at different doses	Patients took part in six sessions. Each patient was exposed to a placebo as well as both drugs at both doses. Participants then completed a battery of test that assessed psychomotor performance.	n=20 (10 male, age=25.7, BMI (kg/m2)=23.8)	Oxycodone (10mg) Oxycodone (20mg) Morphine (30mg) Morphine (60mg)	Both drugs had a similar effect on psychomotor functioning. However, the effects of both drugs were only significant at higher doses. Both oxycodone and morphine at the higher doses produced a similar degree of psychomotor impairment.
Zacny et al. (2012) [37]	United States, Double-blind, randomized, placebo-controlled, triple-dummy, crossover trial	Characterize the effects of oxycodone vs. a placebo	Subjects were given capsules of placebo or drug, and then completed several questionnaires. Psychomotor and cognitive performance was measured with five tests.	n=15; 8 male, mean age=27.0	Oxycodone (10mg)	Oxycodone by itself produced several subjective effects but did not impair psychomotor performance. However, there are trends towards decreased performance with both drugs relative to placebo.

Table 14: Detailed Findings for Original Articles that Address Q1b on Opiates

Author (Year)	Drug(s)	Findings
Amato et al. (2013) [26]	Codeine/paracetamol	1. SDLP (weaving) three doses compared to placebo: F=0.60, n.s. 2. Road exits three doses compared to placebo: F=2.77, n.s. 3. Mean speed three doses compared to placebo: F=0.49, n.s. 4. Reaction time three doses compared to placebo: F=0.88, n.s. 5. Lapses three doses compared to placebo: F=3.48, n.s. 6. KSS (Karolinska Sleepiness Scale) three doses compared to placebo: F=10.50, p=0.01 (less sleepy in lowest compared to middle dose) 7. Perceived driving quality three doses compared to placebo: F=5.11, n.s. 8. VAS (visual analog scale) three doses compared to placebo: F=1.86, n.s.
Baewert et al. (2007) [27]	Methadone	1. Comparing methadone peak/trough groups on MAT (Matrices Test): n.s. 2. Comparing methadone peak/trough groups on Q1 (attention under monotonous circumstances): n.s. 3. Comparing methadone peak/trough groups on FAT (attention flexibility): n.s. 4. Comparing methadone peak/trough groups on LL5 (visual structuring ability): n.s. 5. Comparing methadone peak/trough groups on DR2 (decision and reaction behavior in a dynamic driving environment): n.s. 6. Comparing methadone peak/trough groups on RST3 (Reaction Stress Test): p=0.08, trough > peak 7. Comparing methadone peak/trough groups on TT15 (traffic-specific perception ability; tachistoscope test; correct answers): p=0.04, trough > peak
Gaertner et al. (2006) [28]	Oxycodone	1. Average amount of single tests passed by participants (oxycodone vs. control): 4.0 vs. 4.1, p=0.23 2. Percentage of participants passing all 5 tests (oxycodone vs. control): 39% vs. 56%, n.s. 3. COG (attention test) mean reaction time (seconds) oxycodone vs. control: non-inferior, p<0.01 4. COG attention test score oxycodone vs. control: n.s. 5. DT (determination test, reaction under pressure) mean reaction time (seconds) oxycodone vs. control: n.s. 6. TAVT (visual orientation, tachistoscopic perception) score oxycodone vs. control: non-inferior, p<.05 7. 2-hand (test for motor coordination) score oxycodone vs. control: non-inferior, p<.01 8. VIG (vigilance test) score oxycodone vs. control: non-inferior, p<.01 9. Correlation between daily oxycodone dosage and wrong answers on DT (determination test, reaction under pressure): r=0.45, p=0.01 10. Negative correlation between daily oxycodone dosage and percentile reached in VIG (vigilance test): r=-0.41, p < 0.05 11. Correlation between daily oxycodone dosage and number of wrong answers in COG (attention test): r=0.38, p < 0.05

Gruber et al. (2006) [29]	Methadone	1. Comparison of Stroop Color Word Test scores (baseline/two-month): Color naming: F=1.81, n.s.; Word reading: F=0.62, n.s.; Interference: F=0.08, n.s. 2. Comparison of Rey-O Complex Figures Test (baseline/two-month): Copy condition: F=0.30, n.s.; Immediate condition: F=3.62, p=0.08.; Delay condition: F=5.50, p=0.03 3. Comparison of Rey Auditory Verbal Learning Test (baseline/two-month): F=11.20, p<.01 4. Comparison of Digit Symbol Test (intelligence test) (baseline/two-month): F=5.66, p=0.03 5. Comparison of Controlled Oral Word Association Test (baseline/two-month): Letter fluency: F=3.28, p=.09; Category fluency: F=0.26, n.s. 6. Comparison of Trail Making (measures of attention, speed, and executive function) (baseline/two-month): Trail A: F=2.98, p=.10; Trail B: F=0.05, n.s.
Nilsen et al. (2011) [30]	Codeine	1. Regression analyses (not provided) showed no influence from daily codeine dose on reaction time 2. Reaction time rural test (chronic pain patients without opioids vs. those using opioids): Difference=0.02, p=0.53 3. Reaction time urban test (chronic pain patients without opioids vs. those using opioids): Difference=0.00, p=0.98 4. Missed reactions urban test (chronic pain patients without opioids vs. those using opioids): Incident rate ratio=1.14, p=0.19
Prosser et al. (2009) [31]	Methadone	MM=Methadone Maintained; PA=Protracted Abstinence; CON=Controls 1. Continuous Performance Task (CPT) Correct Hits (MMT/PA/CON): Mean score: 89.9, 118.62, 141.57; p = 0.001 2. Signal detection hit rate (correct response) (MMT/PA/CON): Mean score: 0.581, 0.785, 0.944; Post hoc: CONs>PAs >MMTs; p < .001 3. Signal detection false alarm rate (answering yes on a noise trial) (MMT/PA/COM): Mean score: 2.43×10^{-2}, 6.63×10^{-3}, 8.5×10^{-4}; Post hoc: MMTs > CONs; MMTs > PAs; p < .001 4. Signal detection d' (discriminate signal from noise) (MMT/PA/CON): Mean score: 2.53, 3.66, 4.98; Post hoc: CONs>PAs >MMTs; p < .001
Schumacher et al. (2011a) [32]	Oxycodone, Oxycodone combined with Naloxone, Hydromorphone, Morphine, Fentanyl, Buprenorphine	1. Percent passing 5 VTS (Vienna Test System, computer simulator: above 16th percentile) tests: Patients=8%; Sober controls= 33%. Passing performance on 12 test variables (patients/sober controls): F=7.64, p< .05, controls>patients 2. Compared sum scores (z-transformed values) of all test variables (patients/sober controls): F=14.983, p<0.05, controls>patients 3. 1-sided t-test (patients/sober controls) on DT (Determination Test): p<.01, patients<controls 4. 1-sided t-test (patients/sober controls) on COG (measures attention reaction time): p=0.07 5. 1-sided t-test (patients/sober controls) on TAVTMB (Adaptive Tachistoscopic Traffic Perception Test), number of traffic situations without errors: p<.01, controls>patients 6. 1-sided t-test (patients/sober controls) on LVT (Visual Pursuit Test) number of correct answers in limited time frame: p<.01, controls>patients 7. 1-sided t-test (patients/sober controls) on RT (Reaction Test) average reaction time: p<.05, controls<patients 8. 1-sided t-test (patients/sober controls) on 2-HAND (Two Hand Coordination Test), average time needed to pass the track: p<.05, controls<patients 9. 1-sided t-test (patients/sober controls) on VIGIL (Vigilance Test; patients/controls; one-sided test), total number

		of correct reactions: p=0.41 10. 1-sided t-test (patients/sober controls) on WRBTV (Vienna Risk Taking Test Traffic), average time distance: p<.01, controls>patients
Schumacher et al. (2011b) [33]	Oxycodone, Oxycodone combined with Naloxone, Hydromorphone, Morphine, Fentanyl, Buprenorphine	1. ANOVA for driving performance (patients/sober controls) on SDLP (standard deviation of lateral position): p=0.166 2. ANOVA for driving performance (patients/sober controls) on maintaining speed: p=0.09 3. ANOVA for driving performance (patients/sober controls) on TSA (time to speed adaptation): p=0.09 4. ANOVA for driving performance (patients/sober controls) on gain (amount of overshoot when lead car speeds up): p=0.89 5. ANOVA for driving performance (patients/sober controls) on coherence (correspondence between speed signals): p=0.24 6. ANOVA for driving performance (patients/sober controls) on BRT (brake reaction time): p=0.32 7. ANOVA for subjective measures (patients/sober controls) on performance: p=0.35 (road tracking) and p=0.30 (following) 8. ANOVA for subjective measures (patients/sober controls) on KSS (sleepiness): p=0.02 (road tracking, patients less sleepy) and p=0.06 (following) 9. ANOVA for subjective measures (patients/sober controls) on effort p=0.21 (road tracking) and p=0.09 (following)
Verster & Roth (2011) [38]	Oxycodone/Paracetamol (5/325mg)	1. Differences in scores from placebo on SDLP (weaving): -0.65, n.s. 2. Differences in scores from placebo on tracking test (easy): 0.598, p < .01 3. Differences in scores from placebo on tracking test (hard): 0.719, p < .01 4. Differences in scores from placebo on divided attention test (tracking): 0.536, p < .05 5. Differences in scores from placebo on divided attention test (errors %): 0.257, n.s. 6. Differences in scores from placebo on divided attention test (reaction time): 0.286, n.s. 7. Differences in scores from placebo on Sternberg memory scanning (reaction time): 0.349, n.s. 8. Differences in scores from placebo on Sternberg memory scanning (errors—%): 0.313, n.s.
	Oxycodone/Paracetamol (10/650 mg)	1. Differences in scores from placebo on SDLP (weaving): +1.87, n.s. 2. Differences in scores from placebo on tracking test (easy): 0.246, n.s. 3. Differences in scores from placebo on tracking test (hard): 0.630, p < .01 4. Differences in scores from placebo on divided attention test (tracking): 0.496, p < .05 5. Differences in scores from placebo on divided attention test (errors %): 0.280, n.s. 6. Differences in scores from placebo on divided attention test (reaction time): 0.262, n.s. 7. Differences in scores from placebo on Sternberg memory scanning (reaction time): 0.375, n.s. 8. Differences in scores from placebo on Sternberg memory scanning (errors—%): 0.276, n.s.
Zacny & Gutierrez (2011) [35]	Oxycodone (10 mg)	1. Compared psychomotor task performance (oxycodone/placebo) on DSST (Digit Symbol Substitution Test): n.s. 2. Compared psychomotor task performance (oxycodone/placebo) on ART (Auditory Reaction Time): n.s. 3. Compared psychomotor task performance (oxycodone/placebo) on LRT (Logical Reasoning Test): n.s. 4. Compared psychomotor task performance (oxycodone/placebo) on locally-developed memory recall test: n.s.

Zacny & Lichtor (2008) [36]	Oxycodone (10 mg)	1. Compared psychomotor task performance (drug/placebo) on DSST (Digit Symbol Substitution Test, # symbols drawn): n.s. 2. Compared psychomotor task performance (drug/placebo) on DSST (Digit Symbol Substitution Test, # drawn correctly): n.s. 3. Compared psychomotor task performance (drug/placebo) on Logical Reasoning Test (# statements answered): n.s. 4. Compared psychomotor task performance (drug/placebo) on Eye Hand Coordination (seconds outside circle): n.s.
	Oxycodone (20 mg)	1. Compared psychomotor task performance (drug/placebo) on DSST (Digit Symbol Substitution Test, # symbols drawn): $p<0.05$ (drug fewer symbols) 2. Compared psychomotor task performance (drug/placebo) on DSST (Digit Symbol Substitution Test, # drawn correctly): $p<0.05$ (drug fewer correct) 3. Compared psychomotor task performance (drug/placebo) on Logical Reasoning Test (# statements answered): $p<0.05$ (drug fewer answered) 4. Compared psychomotor task performance (drug/placebo) on Eye Hand Coordination (seconds outside circle): $p<0.05$ (more seconds outside)
	Morphine (30 mg)	1. Compared psychomotor task performance (drug/placebo) on DSST (Digit Symbol Substitution Test, # symbols drawn): n.s. 2. Compared psychomotor task performance (drug/placebo) on DSST (Digit Symbol Substitution Test, # drawn correctly): n.s. 3. Compared psychomotor task performance (drug/placebo) on Logical Reasoning Test (# statements answered): n.s. 4. Compared psychomotor task performance (drug/placebo) on Eye Hand Coordination (seconds outside circle): n.s.
	Morphine (60 mg)	1. Compared psychomotor task performance (drug/placebo) on DSST (Digit Symbol Substitution Test, # symbols drawn): $p<0.05$ (drug fewer symbols) 2. Compared psychomotor task performance (drug/placebo) on DSST (Digit Symbol Substitution Test, # drawn correctly): $p<0.05$ (drug fewer correct) 3. Compared psychomotor task performance (drug/placebo) on Logical Reasoning Test (# statements answered): n.s. 4. Compared psychomotor task performance (drug/placebo) on Eye Hand Coordination (seconds outside circle): n.s.

Zacny et al. (2012) [37]	Oxycodone (10 mg)	1. Compared psychomotor task performance (drug/placebo) on ART (auditory reaction time): n.s. 2. Compared psychomotor task performance (drug/placebo) on DSST (Digit Symbol Substitution Test, # symbols completed): n.s. 3. Compared psychomotor task performance (drug/placebo) on DSST (Digit Symbol Substitution Test, # symbols correct): n.s. 4. Compared psychomotor task performance (drug/placebo) on LRT (Logic Reasoning Test, # statements completed): n.s. 5. Compared psychomotor task performance (drug/placebo) on LRT (Logic Reasoning Test, # statements correct): n.s.

Table 15: Study Design and Conclusions for Original Articles that Address Q1b on Stimulants

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Biederman et al. (2012a) [39]	United States, Randomized, double-blind, parallel-design, placebo controlled	Examine the effects of lisdexamfetamine dimesylate on driving ability as assessed through driving simulator	Baseline (pre-medication) driving simulation assessment and then randomized to receive placebo or active medication for six weeks. Medication was titrated from an initial dose of 30 mg at week one to 50 mg at week two, and to a maximum of 70 mg by week three.	n=61 (62% male, 18-26 years olds who meet the DSMIV criteria for ADHD), average age was 21.6 years	Lisdexamfetamine dimesylate (30 mg week one, 50 mg week two, maximum of 70 mg week 3)	Treatment of ADHD with LDX was associated with faster reaction times and a lower likelihood of having a collision in the driving simulator.
Biederman et al. (2012b) [40]		Examine the effects of lisdexamfetamine dimesylate on driving ability and psychomotor functioning				Treatment of ADHD with LDX resulted in better self-assessment scores particularly within the lapses and errors subgroups. These subgroups are more affected by ADHD then violations so it would follow that medication would better address issues within these subgroups.

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Hjälmdahl et al. (2012) [41]	Sweden, Randomized, double-blind, placebo-controlled, crossover study	Assess the effects using simulated driving of two doses of d-amphetamine and assess the interaction with sleep deprivation	Subjects participated three times, and there were nine conditions varying dose and sleep deprivation. Subjects participated in a 45-minute driving simulator three times each session. Subjects self-reported their sleepiness level using the Karolinska Sleepiness Scale. Blood samples were drawn.	n=18 males, 23–40 years old	d-amphetamine (10mg, 40mg)	Use of d-amphetamine increased self-reported driver alertness. Low dose led to improved driving performance re: crossing-car reaction time, coherence, and delay. High doses were less clear, with the only significant difference relating to crossing-car reaction time. No interaction between dose/sleep deprivation, which suggests administration of d-amphetamine does not compensate for impairment due to fatigue.
Killgore et al. (2008) [42]	United States, Double-blind, randomized, placebo-controlled study, balanced crossover	Study performance on psychomotor vigilance tests before, during, and after administering dexamphetamine after 44 hours of continuous wakefulness	After 44 h of continuous wakefulness, participants received a single double-blind dose of dexamphetamine 20 mg, other stimulants, or placebo. Psychomotor vigilance test (PVT) administered every 2 h for the duration of the waking period (30 tests total including 8 tests post drug) and following 12 h of recovery sleep (four tests).	n= 53 healthy non-smoking adults aged 18–36 (29 men)	Dexamphetamine (20 mg)	The doses tested have significant alerting effects and are effective at countering deficits in PVT performance induced by sleep deprivation for 44–61 h when compared with placebo. The consistency of performance was generally stable and long-lasting for dexamphetamine 20 mg.

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Silber et al. (2006) [43]	Australia, Randomized, double-blind, parallel-design, placebo controlled study	Assess the acute effects of d-amphetamine, d,l-methamphetamine and d-methamphetamine on driving-related cognitive functions	Each participant completed two sessions 2 week apart receiving the placebo once and the experimental dose once. After taking the medication or the placebo they completed a battery of tests assessing neurological, psychomotor, and perceptual speed functioning. Additionally blood and saliva samples were taken.	Study 1: n=20 (10 male, mean age=25.4); Study 2: n=20 (10 male, mean age 24.3); Study 3: n=20 (10 male, mean age=25.4)	Dexamphetamine 0.42-g/kg D,l-methamphetamine 0.42-g/kg D-methamphetamine 0.42-g/kg	Improvements in aspects of attention in d-methamphetamine conditions and some evidence to suggest possible improvements in psychomotor functioning and perceptual speed. Low-dose amphetamine tends to improve aspects of attention with some evidence to suggest enhancement in psychomotor functioning and perceptual speed. Measures of movement estimation are generally improved with amphetamine. No direct demonstrations of amphetamine-related impairments.
Simons et al. (2012) [44]	Germany, Double-blind placebo controlled crossover case-control study	Assessing the effects of dexamphetamine on simulated driving and cognitive performance	One week before the start of their sessions subjects were trained on the driving simulator. Subjects were tested 2 hours after the ingestion of dexamphetamine. The simulator test was 50 minutes and contained urban, rural, and highway driving.	n=16 (12 male, mean age=25.7, mean driving experience=4.3 years)	Dexamphetamine (10 mg)	Participants using 10 mg dexamphetamine alone caused the least number, showed the best performance on divided attention and vigilance tasks but results were not significant. Participants using dexamphetamine alone felt less fatigued, more energetic, more cheerful, less depressed and more clear headed than in any other condition. However, it might have detrimental effects in other performance domains that are relevant to traffic safety, especially at higher doses.

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Sobanksi et al. (2008) [45]	Germany, Case-control study	Determine the impact of methylphenidate on driving for individuals with attention deficit/hyperactivity disorder	Half the patients with ADHD received methylphenidate for 6 weeks. All participants took a series of cognitive tests at the start and end of the experiment. Patients were compared to matched controls.	n=19 adults with ADHD, mean age 34.3. n=27 matched controls, mean age=34.3	Methylphenidate (mean daily dose of 44.3 (30–60 mg) for at least six weeks)	Study demonstrates a benefit of methylphenidate treatment on driving-related cognitive measures and positive effects of methylphenidate medication primarily on visual orientation and visual-motor reaction coordination under high-stress conditions and a marginally significant improvement in keeping track of complex traffic situations.
Verster et al. (2008) [36]	Netherlands, Double blind, placebo-controlled, randomized, two-way, counter-balanced crossover	Examine the effects of methylphenidate on driving performance of adult ADHD patients using an on-the-road test	After three days of no treatment, patients received either their usual methylphenidate dose or placebo and then the opposite treatment after a six to seven day washout period. Patients performed a 100 km driving test during normal traffic, 1.5 h after treatment administration.	n=18 adults with ADHD, 11 men, mean age=38.3 years, mean weight=79.9 kg, and mean height=1.82 m	Methylphenidate (mean: 14.7mg; range 10-30mg)	Driving performance of adult ADHD patients significantly improves when taking methylphenidate. Significant reduction in weaving; self-reports that driving is more relaxed and predictable.

Table 16: Detailed Findings for Original Articles that Address Q1b on Stimulants

Author (Year)	Drug(s)	Findings
Biederman et al. (2012a) [39]	Lisdexamfetamine dimesylate	1. Comparing speed control (placebo/medication): p<0.10, placebo < medication 2. Comparing excessive speeding (placebo/medication): p<0.10, placebo > medication 3. Comparing lateral variation (placebo/medication): p<0.10, placebo > medication 4. Comparing reaction time to surprise events (placebo/medication): F=5.231, p<.05, placebo < medication (0.126 seconds faster/9.1% faster) 5. Comparing likelihood of collision as a result of surprise events (placebo/medication): chi sq=3.9, p<.05, placebo > medication (medication group 67% less likely to have a collision)
Biederman et al. (2012b) [40]		1. Compared DBQ (Driving Behavior Questionnaire) scores, relative effects of LDX vs. placebo over time, total score: p=0.01, LDX>placebo 2. Compared DBQ (Driving Behavior Questionnaire) scores, relative effects of LDX vs. placebo over time, errors: p=0.02, LDX>placebo 3. Compared DBQ (Driving Behavior Questionnaire) scores, relative effects of LDX vs. placebo over time, lapses: p=0.02, LDX>placebo 4. Compared DBQ (Driving Behavior Questionnaire) scores, relative effects of LDX vs. placebo over time, violations: p=0.16, LDX>placebo
Hjälmdahl et al. (2012) [41]	d-amphetamine	1. Mean level of sleepiness using KSS: placebo=5.47, 10 mg=5.00, 40 mg=4.07; all significant 2. ANOVA for driving performance indicator car-crossing reaction time: p=0.001; both doses (2 seconds) different from placebo (2.17 seconds) 3. ANOVA for driving performance indicator SDLP (standard deviation of lateral position): p=0.85 4. ANOVA for driving performance indicator car following coherence: p=0.08; 10 mg dose different from placebo (10 mg > placebo) 5. ANOVA for driving performance indicator car following gain p=0.68 6. ANOVA for driving performance indicator car following delay p=0.04; 10 mg dose different from placebo (10 mg < placebo)
Killgore et al. (2008) [42]	Dexamphetamine	1. Post-drug PVT scores (drug group/placebo group) mean reaction time: F =7.58, p < 0.001 2. Post-drug PVT scores (drug group/placebo group) for speed: F= 14.39, p < 0.001 3. Post-drug PVT scores (drug group/placebo group) for minor lapses: F= 11.82, p < 0.001 4. Post-drug PVT scores (drug group/placebo group) for major lapses: F = 6.11, p = 0.001

Author (Year)	Drug(s)	Findings
Silber et al. (2006) [43]	Dexamphetamine	1. ANOVA for digit span (recall of numbers): F=0.13, n.s. 2. ANOVA for DSST (digit symbol substitution test): F=0.21, n.s. 3. ANOVA for DV (digit vigilance)/accuracy: F=0.48, n.s. 4. ANOVA for DV (digit vigilance)/reaction time: F=4.07, p=0.06 (improvement relative to placebo) 5. ANOVA for Track (visual/motor coordination)/errors: F=1.76, n.s. 6. ANOVA for movement est. (speed and time to contact): F=0.69, n.s. 7. ANOVA for inspection time (perceptual speed): F=3.69, p=0.07 (improvement relative to placebo) 8. ANOVA for Trail Making A&B (visual conceptual/visual motor): F=0.16, n.s.
	D,l-methamphetamine	1. ANOVA for digit span (recall of numbers): F=1.86, n.s. 2. ANOVA for DSST (digit symbol substitution test): F=5.60, p=0.03 (improvement relative to placebo) 3. ANOVA for DV (digit vigilance)/accuracy: F=0.00, n.s. 4. ANOVA for DV (digit vigilance)/reaction time: F=5.17, p=0.04 (improvement relative to placebo) 5. ANOVA for Track (visual/motor coordination)/errors: F=0.72, n.s. 6. ANOVA for movement est. (speed and time to contact): F=0.77, n.s. 7. ANOVA for inspection time (perceptual speed): F=0.02, n.s. 8. ANOVA for Trail Making A&B (visual conceptual/visual motor): F=1.24, n.s.
	D-methamphetamine	1. ANOVA for digit span (recall of numbers): F=0, n.s. 2. ANOVA for DSST (digit symbol substitution test): F=0.05, n.s. 3. ANOVA for DV (digit vigilance)/accuracy: F=8.22, p=0.01 (improvement relative to placebo) 4. ANOVA for DV (digit vigilance)/reaction time: F=3.03, p=0.10 (improvement relative to placebo) 5. ANOVA for Track (visual/motor coordination)/errors: F=0.02, n.s. 6. ANOVA for movement est. (speed and time to contact): F=6.11, p=0.02 (improvement relative to placebo) 7. ANOVA for inspection time (perceptual speed): F=0.05, n.s. 8. ANOVA for Trail Making A&B (visual conceptual/visual motor): F=0.48, n.s.
Simons et al. (2012) [44]	Dexamphetamine	1. ANOVA for SDLP (weaving) drug vs. placebo: n.s. 2. ANOVA for gap acceptance (safety margin) drug vs. placebo: n.s. 3. Percentage of drivers stopping for a red light drug vs. placebo: both 70% 4. ANOVA for collisions drug vs. placebo: n.s. 5. ANOVA for divided attention task drug vs. placebo: n.s. 6. ANOVA for vigilance tracking drug vs. placebo: n.s. 7. ANOVA for KSS (sleepiness) drug vs. placebo: p<.01 (drug users less sleepy)

Author (Year)	Drug(s)	Findings
Sobanksi et al. (2008) [45]	Methylphenidate	1. ANOVA for LL5 (visual orientation, total answers) control group vs. medication group: F=5.47, p<.0.05 (medication higher) 2. ANOVA for Q1 (sustained attention, total answers) control group vs. medication group: F=1.14, n.s. 3. ANOVA for TT15 (track of complex situations) control group vs. medication group: F=1.92, p<0.01 (medication higher) 4. ANOVA for RST3 (reaction behavior phase 1, correct) control group vs. medication group: F=1.25, n.s. 5. ANOVA for RST3 (reaction behavior phase 2, correct) control group vs. medication group: F=5.09, p<0.05 (medication higher) 6. ANOVA for RST3 (reaction behavior phase 3, correct) control group vs. medication group: F=0.73, n.s.
Verster et al. (2008) [38]	Methylphenidate	1. Placebo minus drug difference on SDLP (weaving): 2.3 cm, p=0.004 (drug less weaving) 2. Placebo minus drug difference on speed: 0.5 km/h, p=0.12 3. Self-reported driving quality: p < .05, methylphenidate > placebo 4. Self-reported mental effort: p < 0.05, methylphenidate < placebo

Table 17 show findings pertaining to Q1b from systematic literature reviews.

Table 17: Systematic Literature Reviews that Address Q1b

Author (Year)	Study Objective	Databases Searched	Drug(s) (Dose)	Findings and Conclusions
Barkley & Cox (2007) [46]	Look at effect of stimulant use on driver performance for adults with ADHD	Weekly review of journals indexed in Current Contents (1990-2005)	Methylphenidate (MPH) (10-120 mg); OROS MPH (18-144 mg); mixed amphetamine salts extended release (MAS XR, Adderall® XR) (30 mg)	**Conclusions:** The few studies (n=5) indicate that stimulant medications improve driving performance for drivers with ADHD. **Findings:** 1. Differences in inattentive driving errors, inappropriate braking, and percent of missed stops 2. No differences seen in impulsive driving errors, steering, and off-road driving
Dassanayake et al. (2011) [18]	Examine the association of opioids with driving performance	PubMed and EMBASE (1966-2010)	Opioids (various)	**Conclusions:** Opioid users may be at a higher risk of traffic accidents; however, experimental evidence is scarce. **Findings:** Limited findings based on three studies

Author (Year)	Study Objective	Databases Searched	Drug(s) (Dose)	Findings and Conclusions
ECRI & MANILA (2006) [19]	Investigate the relationship between licit use of Schedule II drugs and CMV crashes	Medline, PubMed (pre-Medline), EMBASE, PsycINFO, CINAHL, TRIS, and the Cochrane library (thru 2006)	Opioids (various)	**Conclusions:** Limited conclusions can be drawn due to a lack of data. **Findings:** Limited findings
			Stimulants	**Conclusions:** Limited conclusions can be drawn due to a lack of data. **Findings:** Limited findings
Fishbain et al. (2003) [20]	To determine what evidence, if any, exists for or against opioid-related driving skill impairment in opioid-dependent/tolerant patients	Medline, Psychological Abstracts, Science Citation Index, and the National Library of Medicine Physician Data Query (PDQ) (1966-2001)	Opioids (various)	**Conclusions:** About a third of 23 identified studies found that patients on stable opioid doses had some impairment of psychomotor abilities. **Findings:** 1. Moderate, generally consistent evidence for no impairment of psychomotor abilities of opioid-maintained patients 2. Inconclusive evidence on multiple studies for no impairment on cognitive function of opioid-maintained patients 3. Strong consistent evidence on multiple studies for no impairment of psychomotor abilities immediately after being given doses of opioids 4. Consistent evidence for no impairment as measured in driving simulators for opioid-maintained patients
Kurita et al. (2008) [47]	Investigate effects of medicinal drugs on traffic safety	PubMed, EMBASE, PsycInfo, CINAHL, and Lilacs (1989-2005)	Opioids (various)	**Conclusions:** Majority of the studies (evidence base is small) showed minor cognitive deficits associated with long-term opioid use. Cognitive impairment was also associated with dose increase and supplemental doses of short-acting opioids. **Findings:** Review of relevant studies found that a majority show minor cognitive deficits in long-term opioid patients

Author (Year)	Study Objective	Databases Searched	Drug(s) (Dose)	Findings and Conclusions
Raes et al. (2008) [23]	Investigate evidence from experimental and field studies of the relationship between drug use, driving impairment, and traffic accidents	ISI Web of Science, PubMed (Medline), Psychinfo and Transport (not provided)	Opioids	**Conclusions:** Opiates acutely cause some cognitive and psychomotor impairment, but these are highly dependent on the type of opiate and the dose administered. The effects are mostly moderate. **Findings:** 1. Morphine tends to slow users' responses, though accuracy is not diminished 2. Fentanyl produces cognitive impairment in doses common in out-patient surgical procedures 3. Methadone maintenance treatment causes impairment, including impairment over and above that associated with heroin dependence, though this can in some cases be explained by other associated risk factors 4. Acute effects of methadone can be avoided by dividing the daily dose.
			Amphetamines	**Conclusions:** Methamphetamine and amphetamine can cause positive stimulating effects on cognitive and psychomotor functions, especially in fatigued or sleep-deprived persons. Negative effects are also observed, such as an overall reduced driving capacity in a simulator during daytime. **Findings:** Experimental studies found both negative and positive effects on performance: positive effects include a decrease in SDLP (weaving) and an increase in psychomotor speed; negative effects include an increase in speed and speed variance and a decrease in the ability to follow a car

Author (Year)	Study Objective	Databases Searched	Drug(s) (Dose)	Findings and Conclusions
Strand et al. (2011) [48]	Review experimental studies on drugs and driving/tasks related to driving for opioids, narcoanalgesics	MEDLINE, EMBASE, and PsycINFO (thru 2007)	Alfentanil/Fentanyl/Remifentanil	**Conclusions:** Suggestive evidence of impairment. **Findings:** 1. A majority of studies show impairments in attention, en/decoding, and visual functions 2. A majority of studies show impairments in psychomotor skills and reaction times for alfentanil and fentanyl
			Codeine	**Conclusions:** Suggestive evidence of impairment. **Findings:** A majority of studies show impairments, included simulated driving
			Hydrocodone/Hydromorphone	**Conclusions:** Suggestive evidence of impairment. **Findings:** 1. Studies found impairment in attention, psychomotor skills, reaction time and visual functions 2. Studies found a dose-effect relationship
			Meperidine (Pethidine)	**Conclusions:** Suggestive evidence of impairment. **Findings:** 1. Studies found impairment in attention, psychomotor skills, reaction time and visual functions 2. Studies found a dose-effect relationship
			Oxycodone	**Conclusions:** Suggestive evidence of impairment. **Findings:** 1. Majority of studies found impairment in attention, divided attention, psychomotor skills, reaction time and visual functions 2. Studies found a dose-effect relationship

Author (Year)	Study Objective	Databases Searched	Drug(s) (Dose)	Findings and Conclusions
			Morphine	**Conclusions:** Suggestive evidence of impairment. **Findings:** Majority of studies found impairments in attention and reaction time, the largest impairment being in the DSST task
Strand et al. (2013) [24]	Review treatment with methadone related to effects on cognitive and psychomotor functions of relevance to driving in experimental studies	MEDLINE, EMBASE, and PsycINFO (thru 2010)	Methadone (2-400 mg)	**Conclusions:** Methadone was confirmed as having impairing potential in opioid-naive subjects. **Findings:** 1. Majority studies show impairments among opioid-naıve subjects after the administration of a comparatively low and single dose of methadone 2. Three studies dealt with single doses to opioid-naive subjects; all three studies found impairment
Wilhelmi & Cohen (2012) [25]	Investigate psychomotor effects of opioids	PubMed (not provided)	Morphine (30-60 mg); Hydrocodone/Acetaminophen (50-20 mg/500-1000 mg); Oxycodone (10-30 mg); Acetaminophen (1000 mg)	**Conclusions:** Current research has established two groups of opioid users: those who have recently begun opioid therapy or who have recently increased their dosage and are likely to demonstrate psychomotor impairment; and chronic users who do not appear to demonstrate significant psychomotor impairment. **Findings:** 1. Majority studies show no psychomotor impairment for stable opioid use patients; 16 of 23 studies supported the conclusion that no psychomotor impairment exists in patients on stable opioid dosages 2. Majority studies show cognitive impairment in stable use opioid patients; 5 of 11 studies that examined whether cognitive function was impaired found no impairment 3. Majority studies show no impairment in driving simulator tasks or on-road driving in chronic opioid therapy patients; 2 of the 3 studies demonstrated that patients performed as well as their control-group counterparts

Findings

Findings are presented for opioids as a group (where the effects of individual drugs were not separately reported) as well as for codeine, codeine/paracetamol, oxycodone, oxycodone/paracetmol, morphine, hydrocodone/hydrimorphone, meperidine, and methadone. For stimulants, findings are presented for amphetamines, methamphetamine, lisdexamfetamine, and methylphenidate. In each section, results are first reported for original research studies, and then for any pertinent systematic reviews. Two of the original research studies share a common data collection effort. Findings are co-reported for shared data sets.

Opioids

Schumacher et al. [32,33] conducted studies comparing patients on stable opioid analgesics to healthy controls. Patients with chronic pain treated with stable doses of opioid analgesics show impairment in driving related skills compared to healthy controls (Schumacher et al. [33]). Patients were less likely to pass a group of five computer tests measuring driving skills than controls, although both groups performed poorly (passed all fitness tests: patients=8%; sober controls= 33%, $p<0.05$). Patients demonstrated impairment compared to sober controls on a sum score of all test variables ($p<0.05$), on the determination test ($p<0.01$), on the adaptive tachistoscopic traffic perception test ($p<0.01$), on a visual pursuit test ($p<0.01$), on a reaction test ($p<0.05$), on a two-hand coordination test ($p<0.05$), and on a risk-taking test ($p<0.01$). There were only two tests without a significant difference, and one of these was marginally significant. However, a similar study design by the same authors comparing patients with sober controls on actual driving did not find any differences (Schumacher et al. [32]).

Six systematic reviews reported results which pertain to opioids in general. Dassanayake et al. [18] found limited evidence. Likewise, ECRI & MANILA did not draw conclusions due to a lack of data [19]. In a larger review of 23 studies, Fishbain et al. [20] found that only about a third of studies find patients on stable opioid doses had some impairment of psychomotor abilities; they conclude there is strong evidence for no impairment in either psychomotor abilities or skills measured using a driving simulator for opioid stable patients. Kurita et al. [47] found that the majority of studies (evidence base is small) showed minor cognitive deficits associated with long-term opioid use, and that impairment was also associated with higher doses of opioids. Raes et al. [23] found that opiates acutely cause some (mostly moderate) cognitive and psychomotor impairment, but effects are highly dependent on the type and dose of opiate. Wilhelmi & Cohen [25] found that there are two groups of opioid users: those who have recently begun opioid therapy or who have recently increased their dosage

and are likely to demonstrate psychomotor impairment, and chronic users who do not appear to demonstrate significant psychomotor impairment.

Codeine

One study looked at the effects of codeine. Nilsen et al. [30] compared healthy patients, pain patients not using codeine, and pain patients using codeine. The study found that codeine does not impair patients with chronic pain over and above the impairment of chronic pain itself related to reaction time in a driving simulator; long-lasting pain may increase reaction time and reduce the ability to respond effectively to stimuli while driving in traffic. Further, no significant differences were found between peak and trough periods for opioid patients.

One systematic review found suggestive evidence of impairment (Strand et. al [48]). A majority of studies show impairment for codeine, including on simulated driving.

Codeine/Paracetamol

One study looked at the effects of three doses of codeine/paracetamol compared to a placebo. Amato et al. [26] found no significant differences between three doses and a placebo on a variety of tests related to weaving, road exits, mean speed, reaction time, lapses, perceived driving quality, and a visual analog scale.

Oxycodone

Four studies looked at the effects of oxycodone. Gaertner et al. [28] was designed as a non-inferiority study to examine patients being treated with controlled release oxycodone with the aim of showing that patients did not perform worse than healthy controls. The non-inferiority delta was set at a level to approximate the effects of driving with BAC=0.05%. Overall, non-inferiority could not be demonstrated on the primary endpoint (matched pairs). However, a weaker test showed that patients did not deviate from controls relative to psychomotor performance. Three additional studies (Zacny & Gutierrez [35], Zacny & Lichtor [36], and Zacny et al. [37]) looked at the effects of 10 mg of oxycodone on various psychomotor tasks. None were significant. Zacny & Lichtor [36] additionally looked at the effects of 20 mg of oxycodone. At this higher dose, all four tests were significant ($p<0.05$) on number of symbols drawn, number drawn correctly, number of statements answered, and hand-eye coordination with codeine subjects showing impairment compared to placebo.

One systematic review found suggestive evidence of impairment (Strand et. al [48]). A majority of studies found impairment in attention, divided attention, psychomotor skills, reaction time and visual functions. Studies also show a dose effect relationship for oxycodone.

Oxycodone/Paracetamol

Only one study looked at the effects of oxycodone/paracetamol. Verster & Roth [38] used a cross-over control trial to compare the effects of oxycodone/paracetamol at two doses (5/325mg and 10/650 mg) to placebo. They found three significant differences at the low dose (on the easy and hard tracking tests ($p<0.01$) and on the divided attention task ($p<0.05$)), and two significant differences for the high dose (on the hard tracking test ($p<0.01$) and on the divided attention task ($p<0.05$)). No differences at either dose were found on tasks related to weaving, reaction time, or memory scanning.

Morphine

Only one study looked specifically at the effects of morphine. Zacny & Lichtor [36] used a cross-over control trial to compare the effects of two doses of morphine (30 mg and 60 mg) on four psychomotor tasks. Findings were only significant at the higher dose and on two of the tasks measuring number of symbols drawn ($p<0.05$) and number drawn correctly ($p<0.05$). In both cases, morphine subjects performed worse than the placebo.

Two systematic reviews examined the effects of morphine. Raes et al. [23] found that morphine tends to slow users' responses, though accuracy is not diminished. Strand et al. [24] found that there is evidence of impairment due to morphine, with the majority of studies finding impairments in attention and reaction time.

Hydrocodone/Hydromorphone and Meperidine (Pethidine)

No original research studies looked at hydrocodone/hydromorphone and meperidine (pethidine). However, one systematic review found suggestive evidence of impairment (Strand et. al [48]). A majority of studies in the review show impairment for codeine, including on simulated driving. For both drugs, studies found impairment in attention, psychomotor skills, reaction time and visual functions. A dose-effect relationship was also observed for both drugs.

Methadone

Three original research studies looked at the effects of methadone. Baewert et al. [27] compared methadone maintained (MM) subjects at peak concentration levels with subjects at trough concentration levels. They found no differences on five tests, a significant difference with peak performing better than trough on traffic perception ability ($p<0.05$), and a marginally significant difference with peak performing better than trough on a reaction stress test ($p<0.10$). Gruber et al. [29] compared a group of patients as they initiated methadone treatment and after two months of treatment. They found that methadone maintenance improved cognitive performance, particularly on tests of learning and memory. There were significant improvements ($p<0.05$) on three tests, marginal improvements ($p<0.10$) on two tests, and no significant differences on five tests. Prosser et al. [31] compared MM patients to controls in protracted abstinence

and healthy controls. They found that subjects with a history of opiate addiction have worse performance on an auditory task than healthy subjects, including fewer correct responses, greater number of errors of omission and commission, and a reduced ability to distinguish signal from noise ($p<0.01$). Subjects receiving methadone replacement therapy have worse performance than do subjects in protracted abstinence ($p<0.01$). This indicates increased brain activity in the healthy comparison group relative to the former opiate addicts and increased brain activity in the protracted absence group relative to the MM group.

One systematic review look at methadone (Strand et al. [24]). The review found that methadone had impairing potential in opioid-naive subjects, based on the results of three studies, all of which showed impairment.

Amphetamines

Amphetamines were examined in four original research studies. Hjälmdahl et al. [41] crossed two dose levels (10 mg and 40 mg) of d-amphetamine with sleep deprivation and performance in a driver simulator. The low dose led to improved driving performance related to crossing-car reaction time ($p<0.01$), coherence ($p<0.10$), and car following delay ($p<0.05$). High doses improved crossing-car reaction time ($p<0.01$). There was no interaction between dose/sleep deprivation, which suggests d-amphetamine does not compensate for impairment due to fatigue. Killgore et al. [42] investigated the effects of dexamphetamine after an extended period of continuous wakefulness. The drug (vs. placebo) group demonstrated enhanced alertness ($p<0.01$) on four psychomotor vigilance tests for reaction time, speed, minor lapses, and major lapses. Silber et al. [43] found no evidence of impairments due to amphetamine in several psychomotor vigilance tests. Medication (vs. placebo) was associated with marginally improved perceptual speed and reaction time test (both $p<0.10$). Simons et al. [44] investigated the effects of 10 mg of dexamphetamine on simulated driving compared to a placebo. While participants taking the drug performed slightly better than placebo, results were not significant. However, they were self-reportedly less sleepy than controls ($p<0.01$).

One systematic review looked at amphetamines and methamphetamines. Raes et al. [23] found methamphetamine and amphetamine can cause positive stimulating effects on cognitive and psychomotor functions, especially in fatigued or sleep-deprived persons. Negative effects are also observed, such as an overall reduced driving capacity in daytime simulator driving. Experimental studies found both negative and positive effects on performance. Positive effects include a decrease in SDLP (weaving) and an increase in psychomotor speed. Negative effects include an increase in speed and speed variance and a decrease in the ability to follow a car.

Methamphetamine

One study investigated the effects of methamphetamines, including D,I-methamphetamine and D-methamphetamine. Silber et al. [43] found no evidence of impairments due to methamphetamine in several psychomotor vigilance tests. Medication (vs. placebo) was associated with improved performance for a digit symbol substitution test and a reaction time test (both $p<0.05$) for D,I-methamphetamine. Medication (vs. placebo) was associated with improved accuracy and speed time to contact (both $p<0.05$) and a trend toward improved reaction time ($p=0.10$) for D-methamphetamine.

One systematic review looked at amphetamines and methamphetamines. Raes et al. [23] found methamphetamine and amphetamine can cause positive stimulating effects on cognitive and psychomotor functions, especially in fatigued or sleep-deprived persons. Negative effects are also observed, such as an overall reduced driving capacity in daytime simulator driving. Experimental studies found both negative and positive effects on performance. Positive effects include a decrease in SDLP (weaving) and an increase in psychomotor speed. Negative effects include an increase in speed and speed variance and a decrease in the ability to follow a car.

Lisdexamfetamine

Two studies using the same dataset reported on the effects of lisdexamfetamine on drivers with ADHD. In both Biederman et al. [39] and Biederman et al. [40] young drivers with ADHD showed improvements compared to placebo. Improvements were recorded on speed control, excess speeding, and weaving (all $p<0.10$) as well as on reaction time to surprise events and likelihood of collision in response to surprise events (both $p<0.05$). Improvements were also noted on scores for a driving behavior questionnaire ($p<0.05$).

Methylphenidate

Two studies investigated the effects of methylphenidate on patients with ADHD. Sobanksi et al. [45] compared adults with ADHD who were taking or not taking medication. They found a benefit of methylphenidate treatment on visual orientation ($p<0.05$), reaction behavior ($p<0.05$), and keeping track of complex traffic situations ($p<0.01$). Verster et al. [38] likewise found that driving performance of adult ADHD patients significantly improved when taking methylphenidate. There was a significant reduction in weaving ($p<0.01$). Drivers on medication also self-reported greater driving quality ($p<0.05$) and that driving required less mental effort ($p<0.05$).

One systematic review looked at the effects of methylphenidate. Barkley & Cox [46] found that the limited available studies suggest that methylphenidate improves driver performance in adults with ADHD.

Conclusions

There is moderate evidence that licit use of opioids negatively impacts indirect measures of driver performance. Studies generally found indicators of impairment, especially for drug-naïve individuals. Impairment was most pronounced on psychomotor vigilance tasks related to pertinent driving skills such as attention, vision, auditory perception, and reaction time. Fewer studies included driving simulators or roadside driving tests; however, where these tests were included, findings tended not to be significant. Findings vary across drug and dose.

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. The handful of relevant studies generally found that stimulants improve performance among adults with ADHD on psychomotor vigilance tests related to reaction time and complex tasks, as well as performance in a driving simulator related to speeding and weaving.

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. The handful of relevant studies generally found limited or no negative outcomes and some small improvements in psychomotor vigilance tasks related to reaction time, coherence, car-following, accuracy, and speed. Effects tend to be dose specific, and may only be present for the use of small or moderate doses. Results were mixed as to whether stimulants can help to counter the effects of sleep deprivation.

Research Question 2

Question 2 asks: 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?

Evidence Base for Question 2

The evidence base for Question 2 consists of n=14 studies, as shown in Figure 4. Findings include n=10 original research articles and n=4 systematic reviews.

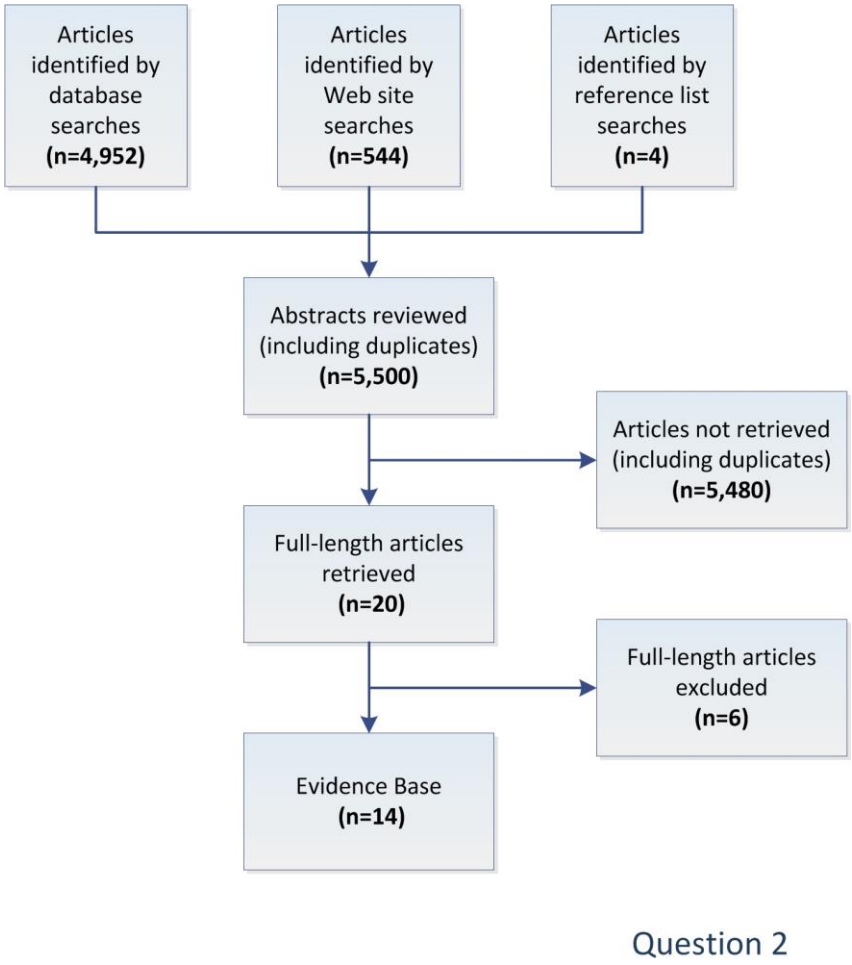
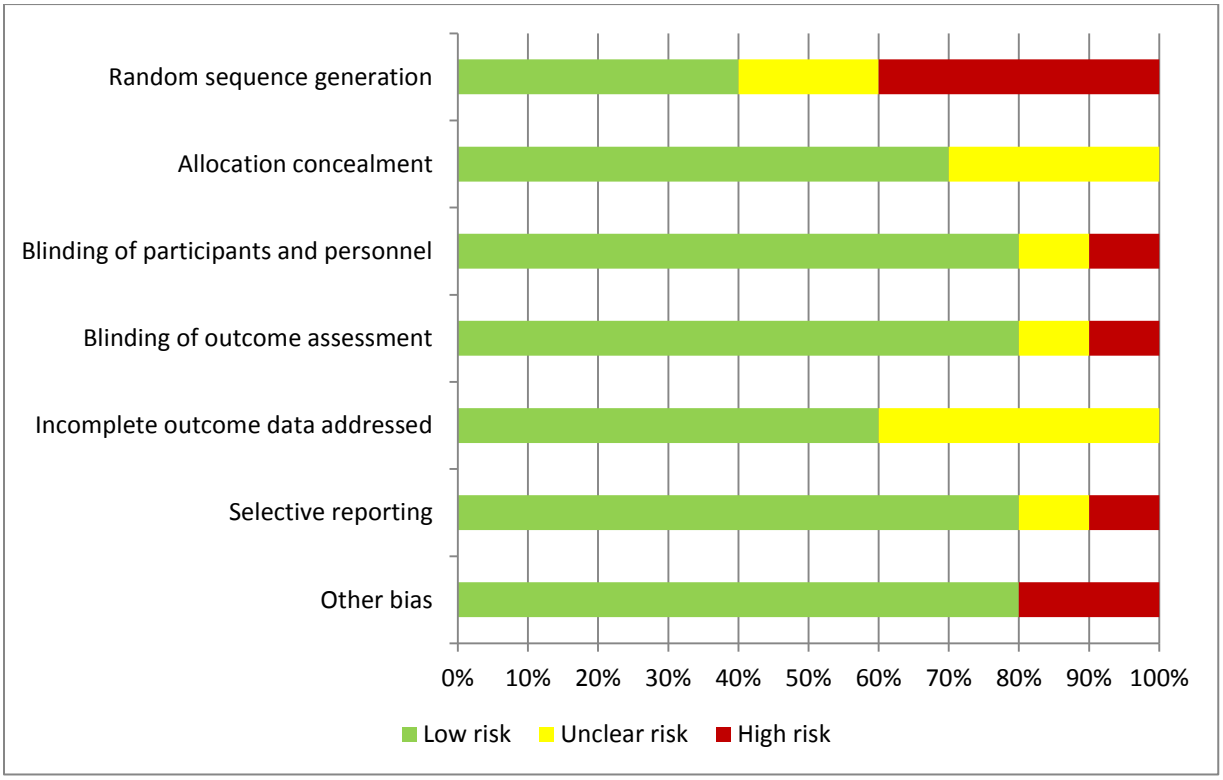


Figure 4: Evidence base, Question 2

Quality of Included Studies

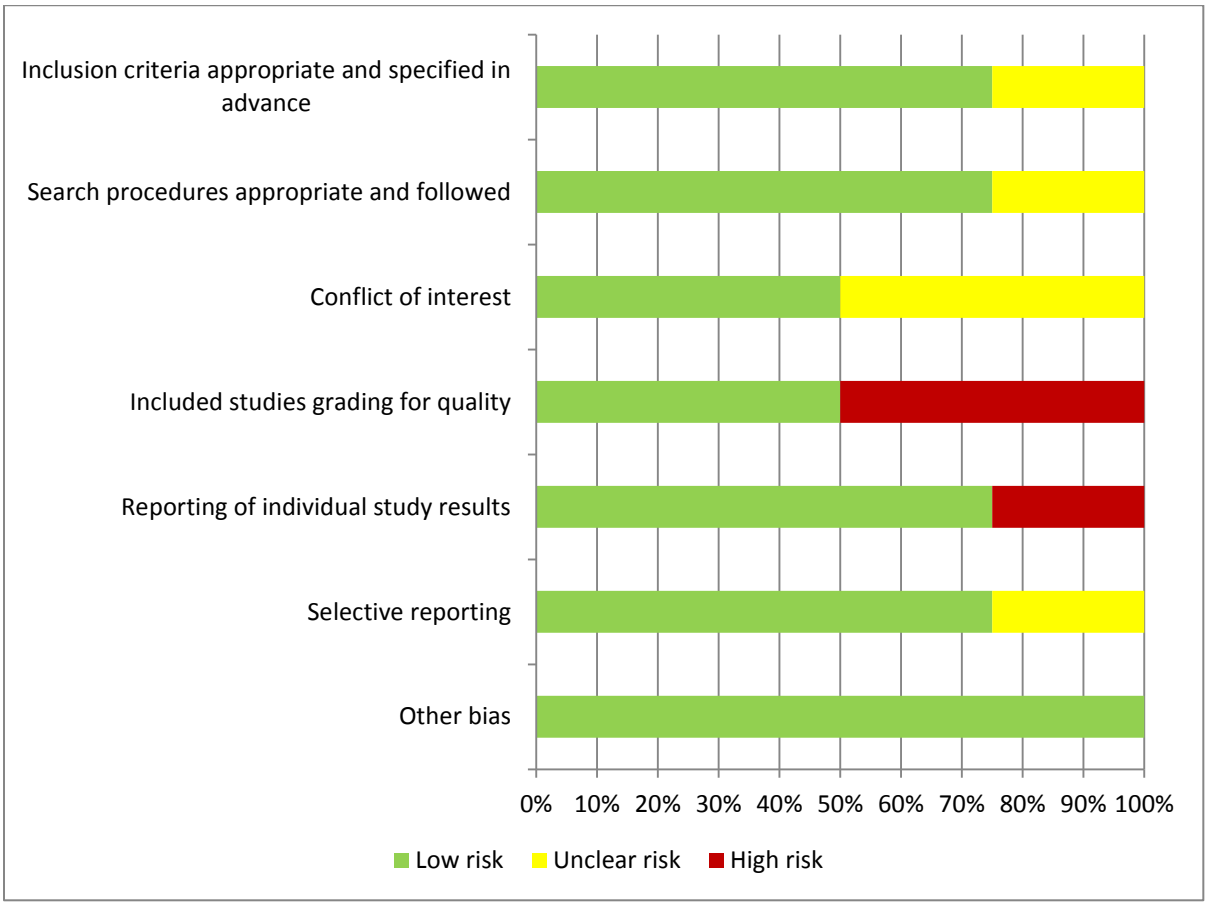
The quality ratings for the original research articles are presented in Table 18. The studies are of moderate quality. The studies are of slightly lower quality related to random sequence generation – this is because some of the studies were registry-based or used another design where drug use was not assigned but occurred naturally.

Table 18: Study Quality for Q2 Original Research Articles



The systematic review articles are likewise of moderate quality, as shown in Table 19. About half graded the included studies for quality, and some did not report all individual study results.

Table 19: Study Quality for Q2 Systematic Review Articles



Summaries of Included Studies

The original research articles that address Q2 are shown in the tables below. Table 20 shows information about the study design and conclusions for original research studies. Table 21 shows detailed findings for each of the original research articles.

Table 20: Study Design and Conclusions for Original Articles that Address Q2

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Amato et al. (2013) [26]	France, Double-blind, randomized, placebo-controlled study, balanced crossover	Evaluate the dose–effect relationship of three usual therapeutic doses of codeine/paracetamol on driving ability, psychomotor performance, and subjective alertness, in link with blood concentrations, in healthy young volunteers	Each participant took part in four sessions spaced two weeks apart. They received one of three doses or placebo; serum concentration was measured at 1 and 4 hours, also completed simulated driving and other tests.	n=16 healthy volunteers (8 men) average age=22.4 years, weight=64.15 kg, and height= 171.80 cm	Codeine	Positive correlations were found between the number of road exits, speed, and mean lateral position and codeine concentrations. No dose effect was found.
					Morphine (metabolite of codeine)	Positive correlations were found between the number of road exits and speed and morphine concentrations. No dose effect was found.

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Baewert et al. (2007) [27]	Austria, Case-control study	Evaluate driving aptitude and traffic-relevant performance at peak and trough medication levels in opioid-dependent patients receiving methadone	Patients on methadone maintenance therapy were matched to controls and subjects were compared on seven traffic psychology tests.	n=20 MM patients (7 male) (10 at peak level (1.5 hours after administration), 10 at trough level (20 hours after administration)), age = 27.9; matched controls (range: n = 3-56) same age, sex, and intelligence	Methadone (52.7 mg ± 21.6)	Patients at trough level showed some impairment compared with patients at peak level when reactive stress tolerance and visual structuring ability were measured. Methadone did not appear to affect orientation in a complex environment, observation capacity, concentration, or attentiveness.
Gjerde et al. (2011) [12]	Norway, Case-control study	To compare the prevalence of drugs in samples from drivers killed in south-eastern Norway with random drivers and to calculate odds ratios for fatally injured drivers	Blood samples from drivers in a fatal road traffic accident were compared to a random sampling of drivers in southeast Norway.	n=204 (fatally injured drivers); controls n=10,540 non-injured drivers	Medical opioids (including Codeine, Morphine, and Methadone) Codeine (above 10 ng/ml)	Use of a single medicinal drug in isolation of other drugs/alcohol does not dramatically increase the rate of being in a fatal accident; however, opioid use is associated with higher risk (although this may occur concurrently with other drugs alcohol). Findings based on serum levels.

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Hjälmdahl et al. (2012) [41]	Sweden, Randomized, double-blind, placebo-controlled, crossover study	Assess the effects using simulated driving of two doses of d-amphetamine and assess the interaction with sleep deprivation	Subjects participated three times; nine conditions varying dose and sleep deprivation. Subjects participated in a 45-minute driving simulator three times each session. Subjects self-reported their sleepiness level using the Karolinska Sleepiness Scale. Blood samples were drawn.	n=18 males, 23–40 years old	d-amphetamine (10mg, 40mg)	Using plasma concentration in the analysis instead of dose yielded the same results.
Nilsen et al. (2011) [30]	Norway, Case-control study	Investigate if codeine influences driving ability in a simulator	Subjects from healthy and non-opioid using pain groups participated in two driving tests with the second test 4 hours after the first. Codeine using patients were tested during peak and trough periods roughly 1 hour after receiving codeine and 5-9 hours after receiving codeine.	n=60 (20 healthy patients, 20 patients with chronic pain not currently prescribed codeine, 20 patients with chronic pain prescribed codeine over long-term)	Codeine (mean serum codeine 225 nM (SD 82) in the peak test period and 70nM at the start of the trough test period)	Serum concentrations were not associated with driving performance among chronic opioid users. The same results were found using dose levels.

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Schumacher et al. (2011b) [33]	Germany, Non-randomized control trial	Assess the risk of having a motor vehicle accident while taking prescribed medications in actual driving conditions	Blood, saliva, and urine samples were taken from all participants. Participants completed a road tracking test on a primary highway, and two weeks later a car following test. Controls completed the driving tests once sober, and once two weeks later with a BAC=0.05%.	n=39 (20 patients; 19 controls)	Morphine equivalency dosage (calculated from blood sample) for Oxycodone, Oxycodone combined with Naloxone, Hydromorphone, Morphine, Fentanyl, or Buprenorphine	Morphine equivalency was not related to SDLP (weaving). The same result was found comparing means of patient and sober controls.
Silber et al. (2006) [43]	Austria, Randomized, double-blind, parallel-design, placebo controlled study	Assess the acute effects of d-amphetamine, d,l-methamphetamine and d-methamphetamine on driving-related cognitive functions	Each participant completed two sessions two week apart receiving the placebo once and the experimental dose once. After taking the medication or the placebo they completed a battery of tests assessing neurological, psychomotor, and perceptual speed functioning. Additionally blood and saliva sample were taken.	Study 1: n=20 (10 male, mean age=25.4); Study 2: n=20 (10 male, mean age 24.3); Study 3: n=20 (10 male, mean age=25.4)	Dexamphetamine (blood/saliva concentrations 120 min: 83/236 ng/ml; 170 min: 98/242 ng/ml; 240 min: 96/260 ng/ml); d,l-methamphetamine (120 min: 90/343 ng/ml; 170 min: 95/475 ng/ml; 240 min: 105/568 ng/ml); d-methamphetamine (120 min: 83/236 ng/ml; 170 min: 67/223 ng/ml; 240 min 59/190 ng/ml)	No significant relations using concentration levels. Findings using dose suggested some improvements in aspects of attention and some evidence to suggest possible improvements in psychomotor functioning and perceptual speed.

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Simons et al. (2012) [44]	Germany, Double-blind placebo controlled crossover case-control study	Assessing the effects of dexamphetamine on simulated driving and cognitive performance	One week before the start of sessions subjects were trained on the driving simulator. Subjects were tested 2 hours after the ingestion of dexamphetamine. The simulator test was 50 minutes and contained urban, rural, and highway driving.	n=16 (12 male, mean age=25.7, mean driving experience=4.3 years)	Dexamphetamine (20.8 ng/ml (range 11.8–40.7))	No significant relations using serum concentration levels. Dose found 10 mg dexamphetamine alone had a trend toward significance (but no significant findings).
Van der Linden et al. (2013) [8]	Belgium, Case-control study	Compare blood concentrations of opioids and amphetamines in seriously injured drivers to non-injured drivers to assess the effects of these drugs	Blood samples were taken from drivers that were seriously injured in a motor vehicle accident and were then compared to blood samples taken from drivers in areas nearby the hospitals where patients were admitted.	n=377 (cases, seriously injured drivers); n=2,750 (controls, roadside respondents)	Codeine	No significant difference (findings based on blood samples for all)
					Methadone	There was a trend for methadone, indicating possibly higher in the roadside group
					Morphine	No significant difference
					Amphetamine	Higher amphetamine concentrations were observed in injured drivers; however, there were limited cases in the roadside survey

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Zacny & Lichtor (2008) [36]	United States, Double-blind, randomized, placebo-controlled crossover study	Compare the effects of oxycodone and morphine on the same subject and at different doses	Patients took part in six sessions. Each patient was exposed to placebo as well as both drugs at both doses. Participants completed a battery of test that assessed psychomotor performance.	n=20 (10 male, age=25.7, BMI (kg/m2)=23.8)	Relative potency expressed as milligrams of morphine necessary to produce the same effect as 1 mg oxycodone	Both doses of the study drugs (oxycodone 10/20 mg and morphine 30/60 mg) increased miosis in a dose-related fashion, and degree of miosis was similar with the two lower doses of the drugs and with the two higher doses of the drugs.

Table 21: Detailed Findings for Original Articles that Address Q2

Author (Year)	Drug(s)	Findings
Amato et al. (2013) [26]	Codeine	1. Correlation between SDLP (weaving) and blood concentration: r=0.059, n.s. 2. Correlation between SDLP (diff to placebo) and blood concentration: r=0.27, p<0.07 3. Correlation between SDS (SD speed) and blood concentration: r=0.05, n.s. 4. Correlation between road exits and blood concentration: r=0.34, p=0.02* 5. Correlation between mean speed and blood concentration: r=0.40, p=0.007* 6. Correlation between mean lateral position and blood concentration: r=0.34, p=0.04* * Results significant or marginally significant using serum vs. other method
	Morphine (metabolite of codeine)	1. Correlation between SDLP (weaving) and blood concentration: r=0.032, p=0.08 2. Correlation between SDLP (diff to placebo) and blood concentration: r=0.33, p=0.08 3. Correlation between SDS (SD speed) and blood concentration: r=0.19, n.s. 4. Correlation between road exits and blood concentration: r=0.57, p=0.001 5. Correlation between mean speed and blood concentration: r=0.51, p=0.005 6. Correlation between mean lateral position and blood concentration: r=0.008, p=n.s.

Author (Year)	Drug(s)	Findings
Baewert et al. (2007) [27]	Methadone	1. Comparing methadone peak/trough groups on MAT (Matrices Test): n.s. 2. Comparing methadone peak/trough groups on Q1 (attention under monotonous circumstances): n.s. 3. Comparing methadone peak/trough groups on FAT (attention flexibility): n.s. 4. Comparing methadone peak/trough groups on LL5 (visual structuring ability): n.s. 5. Comparing methadone peak/trough groups on DR2 (decision and reaction behavior in a dynamic driving environment): n.s. 6. Comparing methadone peak/trough groups on RST3 (Reaction Stress Test): p=0.08, trough > peak 7. Comparing methadone peak/trough groups on TT15 (traffic-specific perception ability; tachistoscope test; correct answers): p=0.04, trough > peak
Gjerde et al. (2011) [12]	Medical opioids	1. Risk (odds ratio) for drivers being fatally injured in a motor vehicle accident while taking medicinal opioids: 4.1 (CI: 1.5-11.5); adjusted= 5.7 (CI: 2.0-16.2) (based on blood samples)
	Codeine	1. Risk (odds ratio) for drivers being fatally injured in a motor vehicle accident while taking codeine: 2.3 (CI: 0.5-9.4); adjusted= 3.0 (CI: 0.7-12.6) (based on blood samples)
Hjälmdahl et al. (2012) [41]	d-amphetamine	1. Primary performance measures show same results using plasma vs. dose: crossing-car reaction time, coherence, and delay showed significant effects (similar) 2. Secondary performance indicator results were also the same using plasma vs. dose (similar)
Nilsen et al. (2011) [30]	Codeine	1. Regression analyses (not provided) showed no influence from codeine or morphine serum concentrations on reaction time (similar) 2. Codeine trough vs. peak reaction time rural test: Difference=0.02, p=0.69 (similar) 3. Codeine trough vs. peak reaction time urban test: Difference=0.02, p=0.68 (similar) 4. Codeine trough vs. peak missed reactions urban test: Incident rate ratio=1.05, p=0.71 (similar)
Schumacher et al. (2011b) [33]	Oxycodone, Oxycodone combined with Naloxone, Hydromorphone, Morphine, Fentanyl, or Buprenorphine	1. Correlation between morphine equivalency dosage and SDLP (weaving): r=0.119, p=0.618 (similar)
Silber et al. (2006) [43]	Dexamphetamine, d,l-methamphetamine, d-methamphetamine	1. No significant relations were found between d-amphetamine levels in blood and performance, with the strongest, an inverse association with reaction time in the Digit Vigilance task [r (19)=−0.44, p=0.06] (similar) 2. No significant relations were found between d,l-methamphetamine levels in blood and performance, with the strongest, a positive associated with reaction time in the Digit Vigilance task [r (19)=0.54, p=0.02] (similar) 3. No significant relations were found between d-methamphetamine levels in blood and performance (some were significant)

Author (Year)	Drug(s)	Findings
Simons et al. (2012) [44]	Dexamphetamine	1. No relevant and/or significant correlations between divided attention scores and dexamphetamine levels in blood could be demonstrated (similar) 2. No relevant and/or significant correlations between vigilance tracking scores and dexamphetamine levels in blood (similar)
Van der Linden et al. (2013) [8]	Codeine	1. Mann Whitney test for difference between injured drivers/roadside drivers testing positive for codeine: -1.12 (n.s.) (based on blood samples) (similar)
	Methadone	1. Mann Whitney test for difference between injured drivers/roadside drivers testing positive for methadone: -1.94 (p=0.053) (based on blood samples) (similar)
	Morphine	1. Mann Whitney test for difference between injured drivers/roadside drivers testing positive for morphine: 0.10 (n.s.) (based on blood samples) (similar)
	Amphetamine	1. Mann Whitney test for difference between injured drivers/roadside drivers testing positive for amphetamine: 2.09 (p=0.037) (based on blood samples) (similar)
Zacny & Lichtor (2008) [36]	Oxycodone, morphine	1. Both doses of the study drugs (oxycodone 10/20 mg and morphine 30/60 mg) increased miosis in a dose-related fashion, and degree of miosis was similar with the two lower doses of the drugs and with the two higher doses of the drugs (similar)

Table 22 show findings pertaining to Q2 from systematic literature reviews.

Table 22: Systematic Reviews that Address Q2

Author (Year)	Study Objective	Databases Searched	Drug(s) (Dose)	Findings and Conclusions
ECRI & MANILA (2006) [19]	Investigate the relationship between licit use of Schedule II drugs and CMV crashes	Medline, PubMed (pre-Medline), EMBASE, PsycINFO, CINAHL, TRIS, and the Cochrane library (thru 2006)	Opioids and Stimulants	**Conclusions:** No data to address the link between serum concentrations, pharmokenetics, and crash risk. **Findings:** Did not find any data to address this relationship.
			Opioids	**Conclusions:** The magnitude of acute cognitive or psychomotor functional deficits observed among opioid-naïve individuals following administration of a Schedule II opioid is correlated with the serum level of the drug (Strength of Evidence: Strong). **Findings:** Based on results of three studies

Author (Year)	Study Objective	Databases Searched	Drug(s) (Dose)	Findings and Conclusions
			Opioids	**Conclusions:** The pharmacokinetics of Schedule II opioids (morphine, fentanyl, and meperidine) are closely correlated with temporal changes in measures of cognitive and psychomotor function in healthy opioid-naïve individuals (Strength of Evidence: Strong). **Findings:** Based on results of three studies
Kurita et al. (2008) [47]	Better understand effects of opioids on cognitive function in cancer pain patients	PubMed, EMBASE, PsycInfo, CINAHL, and Lilacs (1989-2005)	Opioids (various)	**Conclusions/Findings:** Only one study out of three total found associations between concentrations of morphine and its metabolites and cognitive deficits.
Raes et al. (2008) [23]	Investigate evidence of the relationship between drug use, driving impairment, and traffic accidents	ISI Web of Science, PubMed (Medline), Psychinfo and Transport (not provided)	Amphetamines	**Conclusions:** Limited data suggests a relationship with blood concentrations. **Findings:** A positive relationship was found between blood amphetamine concentration and impairment, but it reached a ceiling at concentrations of 270–530 ng/ml
Strand et al. (2011) [48]	Review experimental studies on drugs and driving/tasks related to driving for opioids, narcoanalgesics	MEDLINE, EMBASE, and PsycINFO (thru 2007)	Alfentanil/Fentanyl/Remifentanil; Codeine; Hydrocodone/Hydromorphone; Meperidine (Pethidine); Oxycodone Morphine	**Conclusions:** Evidence of impairment related to blood concentrations. **Findings:** Dose and blood drug concentration related effects were found for all three drug types
			Morphine	**Conclusions:** No evidence of impairment related to blood concentrations. **Findings:** Review of relevant studies found no clear concentration-effect relations

Findings

The original research studies that included results both by serum levels and using another approach (e.g., by dose or prescription records) were largely in concordance. The majority of the studies identified [8,30,33,36,41,43,44] reported similar results using serum concentrations as they found via other measures. One exception was Amato et al. [26] which found three additional significant results for codeine using serum levels. Additionally, the authors were able to investigate how quickly codeine metabolizes by measuring morphine concentrations; this allowed for the detection of an additional marginally significant difference for weaving ($r=0.032$, $p=0.08$), which was not present when looking at codeine alone.

Four systematic reviews investigated the relationship between serum levels and impairment. ECRI & MANILA [19] concluded that serum levels are positively associated with impairment of opioid naïve individuals. Kurita et al. [47] found one study (of three) linked blood morphine levels to cognitive deficits. Raes et al. [23] found a positive relationship between blood amphetamine concentration and impairment, but this relationship had a ceiling effect. Finally, Strand et al. [48] found evidence of a concentration relationship for a variety of opioids, but not for morphine.

Conclusions

There is moderate evidence that the effects of opioids and stimulants are measureable by serum levels. Findings were generally consistent across studies that serum levels are comparable to other methods in investigating relationships between licit drug use and driving impairment. However, this relationship likely exists for only certain Schedule II medications, and may also be subject to floor or ceiling effects. Investigating relationships by serum level allows for a better understanding of possible variation due to differences in how individuals metabolize medicines.

Research Question 3

Question 3 asks: Do the effects (as found in question 1) 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)?

Evidence Base for Question 3

The evidence base for Question 3 consists of n=19 studies, as shown in Figure 5. Findings include n=12 original research articles and n=7 systematic reviews.

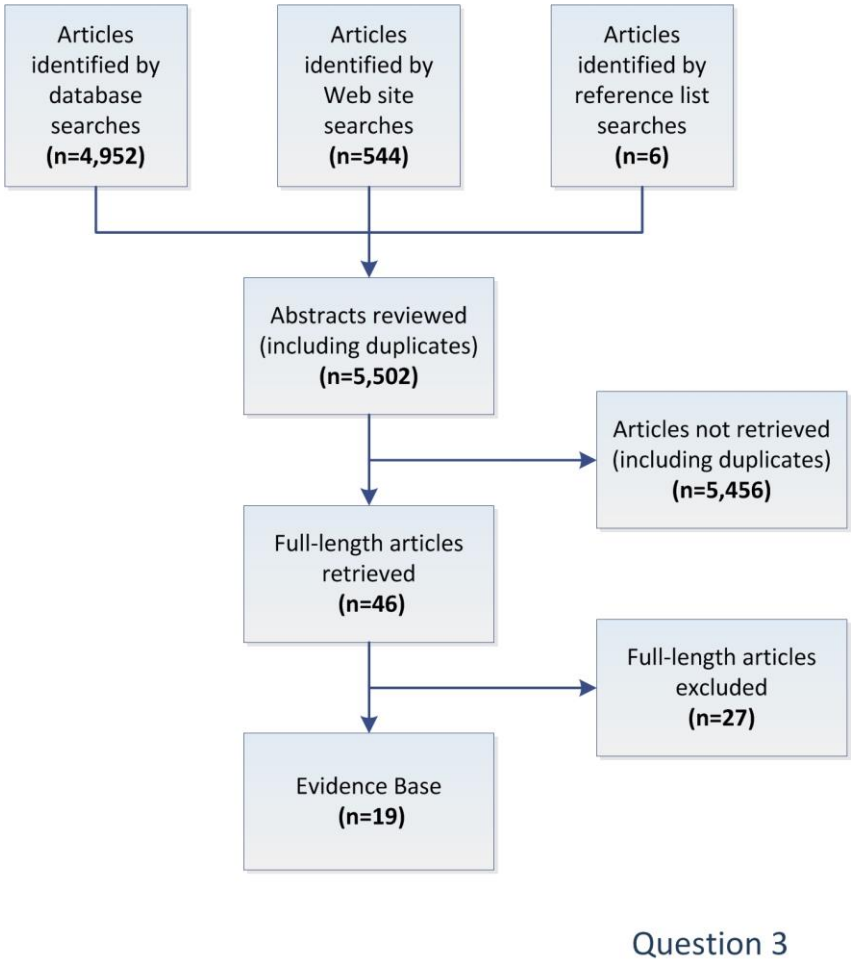
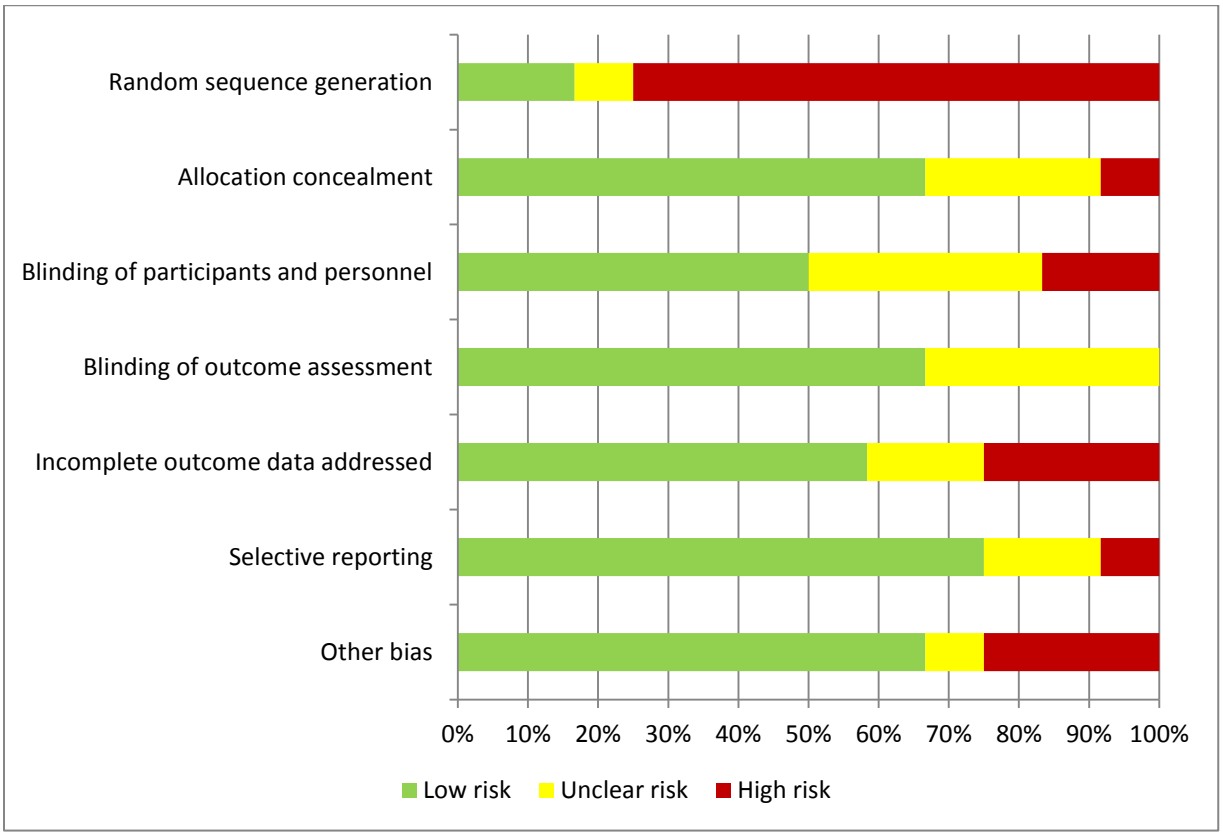


Figure 5: Evidence base, Question 3

Quality of Included Studies

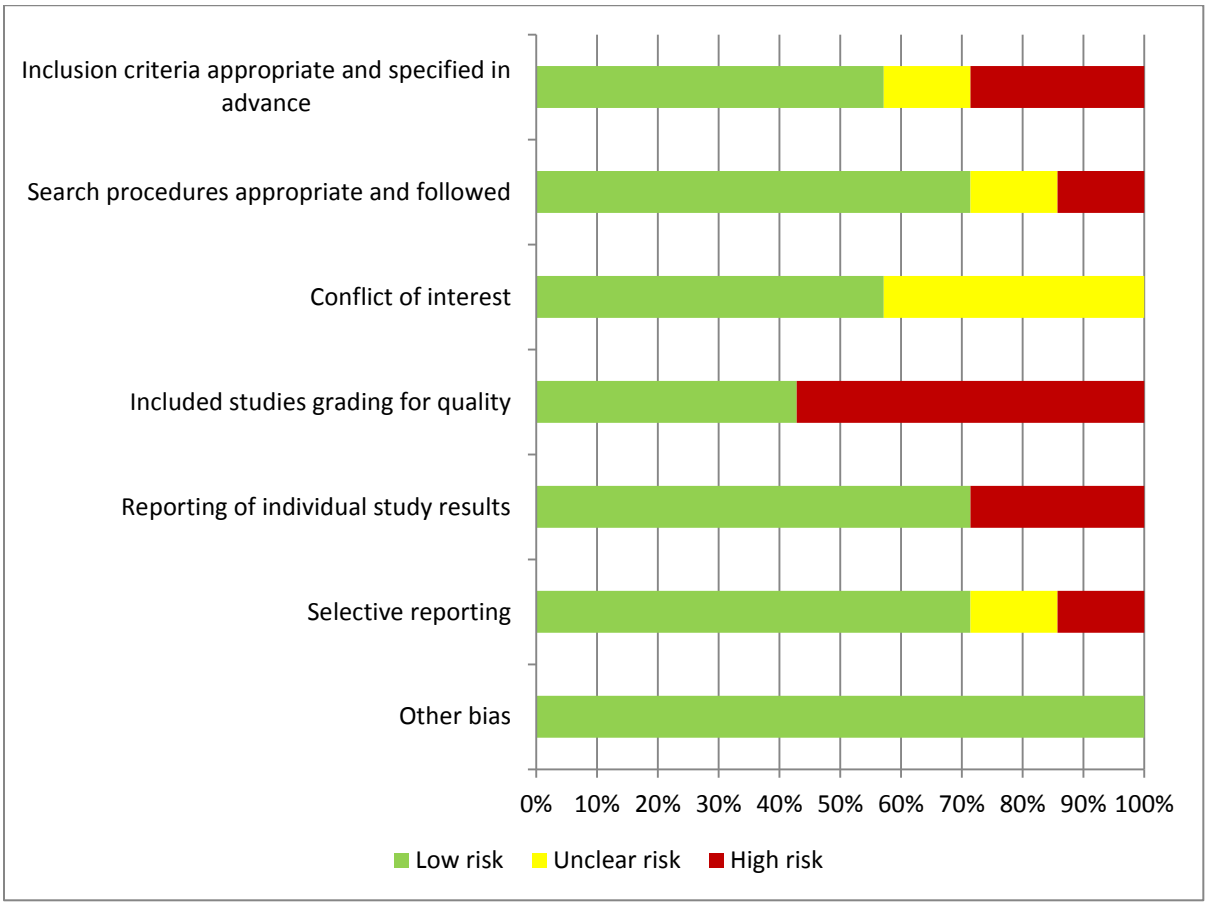
The quality ratings for the original research articles are presented in Table 23. Very few of the studies investigating this question used random assignment to condition. Many of the studies were registry-based or used another design where drug use was not assigned but occurred naturally.

Table 23: Study Quality for Q3 Original Research Articles



The systematic review articles are likewise of moderate quality, as shown in Table 24. About half graded the included studies for quality, and some did not report all individual study results.

Table 24: Study Quality for Q3 Systematic Review Articles



Summaries of Included Studies

The original research articles that address Q3 are shown in the tables below. Table 25 shows information about the study design and conclusions for original research studies on drug interactions. Table 26 shows detailed findings for each of the original research articles on drug interactions. Table 27 shows information about the study design and conclusions for original research studies on stable use. Table 28 shows detailed findings for each of the original research articles on stable use.

Table 25: Study Design and Conclusions for Original Articles that Address Q3 on Drug Interactions

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Amato et al. (2013) [26]	France, Double-blind, randomized, placebo-controlled study, balanced crossover	Evaluate the dose–effect relationship of three usual therapeutic doses of codeine/paracetamol on driving ability, psychomotor performance, and subjective alertness, in link with blood concentrations, in healthy young volunteers	Each participant took part in four sessions spaced two weeks apart. They received one of three doses or placebo; serum concentration was measured at 1 and 4 hours, also completed simulated driving and other tests.	n=16 healthy volunteers (8 men) average age=22.4 years, weight=64.15 kg, and height= 171.80 cm	Codeine/paracetamol (20/400 mg, 40/800 mg, 60/1200 mg)	Found no dose effect with usual therapeutic doses of codeine/paracetamol in a single intake and did not show impairment of driving or vigilance.
Bachs et al. (2009) [1]	Norway, Cohort study	Examine whether a driver who has filled a prescription for codeine is at increased risk of being involved in a	Analysis of prescription drug dispending records and automobile crash records over a 33-month study period. Data from Norwegian Prescription	n=3.1 million; all inhabitants of Norway 18+ living in Norway 2004–2006 were included	Codeine (two groups 60 DDD (defined daily dose) or more, <60DDD)	SIR for codeine consumption is elevated and highest for those 35-54 and for high consumers; however, this decreases when co-prescriptions are excluded

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
		road accident resulting in injury to persons	Database (NorPD), the Norwegian Road Accident Registry, and the Norwegian Central Population Registry. Calculated Standardized Incidence Ratio (SIR), taking sex and age into consideration.		Codeine nonregular users (no previous prescription 180 days)	SIR was not increased for non-regular users (no previous use past 180 days); codeine use only increased SIR when co-prescriptions were included
Gibson et al. (2009) [11]	UK, Case-crossover and case-series analyses	Investigate the impact of using various drugs on the risk of motor vehicle crashes	Case-crossover: At-risk period = 4-weeks prior to crash. 5 successive 4-week periods were used starting prior to at-risk period. Exposure was defined by prescription. Case-series: Records were grouped according to the interval between prescriptions. Outcome of interest was the first crash. Available follow-up time was classified based on exposure and whether changes in risk of crash are short-lived, develop over time, or are constant.	n=7,300 individuals, 18-74 with at least one crash a year, data from The Health Improvement Network, prospectively collected primary care records with prescription information from 255 general practices	Drug-Drug Combination (compound opioid analgesics/acetaminophen)	Risk of motor vehicle crash is increased by the use of compound analgesic preparations containing acetaminophen and an opioid for the duration of their usage, the risk decreasing once the medication is discontinued; use of acetaminophen/opioid compound analgesic preparations associated with a raised risk of motor vehicle crash in the first 4 weeks of treatment, which increased with extended exposure before decreasing to unity by the second 12-week post exposure period; similar to results for opioids alone

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Verster & Roth (2011) [34]	Netherlands, Double-blind placebo controlled crossover case-control study	Double-blind placebo controlled crossover case-control study	Assess the effect of medicinal opiates using on-the-road driving tests and psychometric tests	Treatment sequences randomized. One hour after treatment, a driving test was administered. Approximately 2.5 hours after intake tests were performed. Test days separated by a seven day washout period.	Oxycodone/Paracetamol (5/325mg) Oxycodone/Paracetamol (10/650 mg)	Relative to placebo, oxycodone/paracetamol negatively impacts tracking test and divided attention tasks.

Table 26: Detailed Findings for Original Articles that Address Q3 on Drug Interactions

Author (Year)	Drug(s)	Findings
Amato et al. (2013) [26]	Codeine/paracetamol	1. SDLP (weaving) three doses compared to placebo: F=0.60, n.s. 2. Road exits three doses compared to placebo: F=2.77, n.s. 3. Mean speed three doses compared to placebo: F=0.49, n.s. 4. Reaction time three doses compared to placebo: F=0.88, n.s. 5. Lapses three doses compared to placebo: F=3.48, n.s. 6. KSS (Karolinska Sleepiness Scale) three doses compared to placebo: F=10.50, p=0.01 (less sleepy in lowest compared to middle dose) 7. Perceived driving quality three doses compared to placebo: F=5.11, n.s. 8. VAS (visual analog scale) three doses compared to placebo: F=1.86, n.s.

Author (Year)	Drug(s)	Findings
Bachs et al. (2009) [1]	Codeine	1. Risk (SIR) for traffic accidents after exposure to codeine: 1.9 (CI: 1.6-2.2); Co-prescription excluded: 1.3 (CI: 1.0-1.6) 2. Risk (SIR) for males being involved in traffic accidents after exposure to codeine: 2.0 (CI: 1.6-2.4); Co-prescription excluded: 1.3 (CI: 0.9-1.7) 3. Risk (SIR) for females being involved in traffic accidents after exposure to codeine: 1.8 (CI: 1.4-2.3); Co-prescription excluded: 1.3 (CI: 0.9-1.8) 4. Risk (SIR) for traffic accidents after exposure to codeine (codeine high consumers): 2.9 (CI: 2.3-3.6); Co-prescription excluded: 0.9 (CI: 0.5-1.3) 5. Risk (SIR) for traffic accidents after exposure to codeine (males 35-54): 2.5 (CI: 1.9-3.2); Co-prescription excluded: 1.5 (CI: 1.0-2.1) 6. Risk (SIR) for traffic accidents after exposure to codeine (females 35-54): 2.0 (CI: 1.4-2.6); Co-prescription excluded: 1.7 (CI: 1.0-2.4)
Gibson et al. (2009) [11]	Compound opioid analgesics/acetaminophen	1. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking acetaminophen/opioid compound analgesics (4 week period up to and including the date of the prescription): 21.22 (99% CI: 20.27-22.20) 2. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking acetaminophen/opioid compound analgesics (4-week period following the first prescription of a course of treatment): 2.06 (99% CI: 1.84-2.32) 3. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking acetaminophen/opioid compound analgesics (remainder of exposed time): 2.66 (99% CI: 2.40-2.95) 4. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking acetaminophen/opioid compound analgesics (12-week period following the end of exposure): 1.10 (99% CI: 1.00-1.21) 5. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking acetaminophen/opioid compound analgesics (second 12-week period following the end of exposure): 0.94 (99% CI: 0.85-1.05)
		1. Risk (odds ratio) for being involved in a motor vehicle crash while taking acetaminophen/opioid compound analgesics (29-56 days before motor vehicle crash): 1.16 (99% CI: 1.04-1.29) 2. Risk (odds ratio) for being involved in a motor vehicle crash while taking acetaminophen/opioid compound analgesics (57-84 days before motor vehicle crash): 1.23 (99% CI: 1.10-1.38) 3. Risk (odds ratio) for being involved in a motor vehicle crash while taking acetaminophen/opioid compound analgesics opioids (85-112 days before motor vehicle crash): 1.26 (99% CI: 1.13-1.42) 4. Risk (odds ratio) for being involved in a motor vehicle crash while taking acetaminophen/opioid compound analgesics (113-140 days before motor vehicle crash): 1.26 (99% CI: 1.12-1.41) 5. Risk (odds ratio) for being involved in a motor vehicle crash while taking acetaminophen/opioid compound analgesics (141-168 days before motor vehicle crash): 1.23 (99% CI: 1.10-1.38)

Author (Year)	Drug(s)	Findings
Verster & Roth (2011) [34]	Oxycodone/Paracetamol (5/325mg)	1. Differences in scores from placebo on SDLP (weaving): -0.65, n.s. 2. Differences in scores from placebo on tracking test (easy): 0.598, p < .01 3. Differences in scores from placebo on tracking test (hard): 0.719, p < .01 4. Differences in scores from placebo on divided attention test (tracking): 0.536, p < .05 5. Differences in scores from placebo on divided attention test (errors %): 0.257, n.s. 6. Differences in scores from placebo on divided attention test (reaction time): 0.286, n.s. 7. Differences in scores from placebo on Sternberg memory scanning (reaction time): 0.349, n.s. 8. Differences in scores from placebo on Sternberg memory scanning (errors—%): 0.313, n.s.
	Oxycodone/Paracetamol (10/650 mg)	1. Differences in scores from placebo on SDLP (weaving): +1.87, n.s. 2. Differences in scores from placebo on tracking test (easy): 0.246, n.s. 3. Differences in scores from placebo on tracking test (hard): 0.630, p < .01 4. Differences in scores from placebo on divided attention test (tracking): 0.496, p < .05 5. Differences in scores from placebo on divided attention test (errors %): 0.280, n.s. 6. Differences in scores from placebo on divided attention test (reaction time): 0.262, n.s. 7. Differences in scores from placebo on Sternberg memory scanning (reaction time): 0.375, n.s. 8. Differences in scores from placebo on Sternberg memory scanning (errors—%): 0.276, n.s.

Table 27: Study Design and Conclusions for Original Articles that Address Q3 on Stable Use

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Gaertner et al. (2006) [28]	Germany, Case-control, non-inferiority	Examine cognitive and psychomotor effects of oxycodone in patients receiving long-term treatment; non-inferiority level set equivalent to BAC=0.05%	Each participant was asked to perform a battery of tests; medication usage was assessed from blood sample given before each session.	n=30 adult outpatients suffering from non-cancer pain and responsive to opioids + n=90 healthy controls	Oxycodone (controlled release), average dose=63 mg	Failed to demonstrate statistical non-inferiority of patients receiving oxycodone compared with controls (using as the delta level impairment caused by BAC=0.05). Using weaker statistical analyses, patients' psychomotor performance did not deviate significantly from age-independent control group.

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Gibson et al. (2009) [11]	UK, Case-crossover and case-series analyses	Investigate the impact of using various drugs on the risk of motor vehicle crashes	Case-crossover: At-risk period = 4-weeks prior to crash. 5 successive 4-week periods were used starting prior to at-risk period. Exposure was defined by prescription. Case-series: Records were grouped according to the interval between prescriptions. Outcome of interest was the first crash. Available follow-up time was classified based on exposure and whether changes in risk of crash are short-lived, develop over time, or are constant.	n=7,300 individuals, 18-74 with at least one crash a year, data from The Health Improvement Network, prospectively collected primary care records with prescription information from 255 general practices	Dihydrocodeine (dosages vary/not specified) Codeine phosphate (dosages vary/not specified) Morphine (dosages vary/not specified)	Risk of motor vehicle crash is increased by the use of opioids for the duration of their usage, the risk decreasing once the medication is discontinued; the initiation of opioid treatment was associated with an increased risk of motor vehicle crash that persisted throughout the remainder of treatment but was not observed after withdrawal of treatment
Gomes et al. (2013) [13]	Canada, Nested case-control	To characterize the relationship between opioid dose and risk of road trauma	Case and control information was retrieved via prescription drug registries and incidence of road trauma was determined from National Ambulatory Care Reporting System. Patients were separated by opioid dose level.	n=10,600 (all prescribed opioids; cases experienced road trauma, matched controls did not), mean age=45.8, male=51.4%; sub analysis of drivers only, n=2,428 cases + n=2,428 controls	Codeine, Morphine sulfate, Oxycodone or Hydromorphone Hydrochloride, and transdermal Fentanyl patches (all drugs were converted into morphine equivalent (MEQ))	No significant difference was found between new opioid user and long-term users (includes both drivers and non-drivers); in general, there was an increased risk of road trauma correlated to increase opiate dose compared with patients prescribed very low opioid doses

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Nilsen et al. (2011) [30]	Norway, Case-control study	Investigate if codeine influences driving ability in a simulator	Subjects from healthy and non-opioid using pain groups participated in two driving tests with the second test 4 hours after the first. Codeine using patients were tested during peak and trough periods roughly 1 hour after receiving codeine and 5-9 hours after receiving codeine.	n=60 (20 healthy patients, 20 patients with chronic pain not currently prescribed codeine, 20 patients with chronic pain prescribed codeine over long-term)	Codeine (median dose 180 mg)	Codeine does not impair patients with chronic pain over and above the impairment of chronic pain itself; long-lasting pain may increase the reaction time and reduce the ability to respond effectively to relevant stimuli while driving in traffic. There was no significant difference between chronic pain patients using and not using opioids. Furthermore there was no significant difference between peak and trough periods for opioid patients.
Prosser et al. (2009) [31]	United States, Case-control study	Assess the functioning of sustained attention in subjects with a history of opiate dependence using clinical measures and positron emission tomography (PET)	A test of auditory sustained attention was administered. Simultaneous measurement of regional glucose metabolism was made by flourodeoxyglucose PET. Subjects groups were compared on the measures of sustained attention and regional cerebral glucose metabolism.	n=10 MM opiate-dependent (9 male), mean age= 40.6 [MM]. n=13 opiate dependent (11 male) in protracted abstinence, mean age 41.23 [PA]. n=14 healthy volunteers (10 male), mean age = 33.0 [CON]	Methadone	Subjects with a history of opiate addiction have worse performance on an auditory task than healthy subjects: fewer correct responses, greater number of errors of omission and commission, and a reduced ability to distinguish signal from noise. Subjects receiving MM therapy have worse performance than do subjects in protracted abstinence.

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Ravera & De Gier (2010) [16]	Netherlands, Case-control study	Assess the association between traffic accident risk and psychotropic medication exposure	Records from three separate databases (pharmacy records, traffic accident records, and driver's license records) were linked. For each accident four controls who did not have an accident were linked based on demographic information. Researchers compared the prevalence of opioids between the two groups.	n=4,784 cases (had a traffic accident between 2000 and 2007); n=19,136 controls (adults who had a driving license and had no traffic accident during the study period)	Opioids (all drugs combined)	New users taking opioids were not at higher risk than chronic users of being in an accident; drivers overall were not at higher risk
Schumacher et al. (2011a) [32]	Germany, Non-randomized control trial	Assess driving impairment of patients on stable opioid analgesic treatments in computerized driving tasks	Blood, saliva, and urine samples were taken from all patients. All participants completed the Vienna Test System plus three additional tests to measure driver fitness related skills. All participants gave self-assessments on the KSS (to measure sleepiness). Controls completed the driving tests once sober, and once two weeks later with a BAC=0.05%.	n=26 patients recruited from the pain outpatient department (58% male, mean age=54.00); n=21 healthy volunteers (62% male, mean age=43.10)	Oxycodone (10 mg/day, slow release), Oxycodone combined with Naloxone (10 mg/day, slow release), Hydromorphone (4 mg /day, slow release) or Morphine (20 mg/day, slow release), Fentanyl (12 g/h, transdermal), Buprenorphine (10g/h, transdermal) [Patients had been treated with one of these]	Patients with chronic pain treated with stable doses of opioid analgesics show impairment in driving related skills compared to healthy controls.

Author (Year)	Location and Design of Study	Study Objective	Procedures/Protocol	Sample Size and Demographics	Drug(s) (Dose)	Conclusions
Schumacher et al. (2011b) [33]	Germany, Non-randomized control trial	Assess the risk of having a motor vehicle accident while taking prescribed medications in actual driving conditions	Blood, saliva, and urine samples were taken from all participants. Participants completed a road tracking test on a primary highway, and two weeks later a car following test. Controls completed the driving tests once sober, and once two weeks later with a BAC=0.05%.	n=39 (20 patients; 19 controls)	Oxycodone (10 mg/day, slow release), Oxycodone combined with Naloxone (10 mg/day, slow release), Hydromorphone (4 mg /day, slow release), Morphine (20 mg/day, slow release), Fentanyl (12 g/h, transdermal), or Buprenorphine (10g/h, transdermal) [Patients had been treated with one of these for at least 4 weeks]	Patients on stable doses of opioids did not differ in driving skills from sober controls.
Sobanksi et al. (2008) [45]	Germany, Case-control study	Determine the impact of methylphenidate on driving for individuals with attention deficit/hyperactivity disorder	Half the patients with ADHD received methylphenidate for 6 weeks. All participants took a series of cognitive tests at the start and end of the experiment. Patients were compared to matched controls.	n=19 adults with ADHD, mean age 34.3. n=27 controls matched to the demographic information, mean age=34.3	Methylphenidate (mean daily dose of 44.3 (30–60 mg) for at least six weeks)	Study demonstrates a benefit of methylphenidate treatment on driving-related cognitive measures and positive effects of methylphenidate medication primarily on visual orientation and visual-motor reaction coordination under high-stress conditions and a marginally significant improvement in keeping track of complex traffic situations.

Table 28: Detailed Findings for Original Articles that Address Q3 on Stable Use

Author (Year)	Drug(s)	Findings
Gaertner et al. (2006) [28]	Long-term Oxycodone	1. Average amount of single tests passed by participants (oxycodone vs. control): 4.0 vs. 4.1, p=0.23 2. Percentage of participants passing all 5 tests (oxycodone vs. control): 39% vs. 56%, n.s. 3. COG (attention test) mean reaction time (seconds) oxycodone vs. control: non-inferior, p<0.01 4. COG attention test score oxycodone vs. control: n.s. 5. DT (determination test, reaction under pressure) mean reaction time (seconds) oxycodone vs. control: n.s. 6. TAVT (visual orientation, tachistoscopic perception) score oxycodone vs. control: non-inferior, p<.05 7. 2-hand (test for motor coordination) score oxycodone vs. control: non-inferior, p<.01 8. VIG (vigilance test) score oxycodone vs. control: non-inferior, p<.01 9. Correlation between daily oxycodone dosage and wrong answers on DT (determination test, reaction under pressure): r=0.45, p=0.01 10. Negative correlation between daily oxycodone dosage and percentile reached in VIG (vigilance test): r=-0.41, p < 0.05 11. Correlation between daily oxycodone dosage and number of wrong answers in COG (attention test): r=0.38, p < 0.05
Gibson et al. (2009) [11]	Dihydrocodeine	1. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking dihydrocodeine (4 week period up to and including the date of the prescription): 11.73 (99% CI: 10.21-13.49) 2. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking dihydrocodeine (4-week period following the first prescription of a course of treatment): 1.60 (99% CI: 1.14-2.25) 3. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking dihydrocodeine (remainder of exposed time): 1.05 (99% CI: 0.78-1.42) 4. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking dihydrocodeine (12-week period following the end of exposure): 1.15 (99% CI: 0.91-1.47) 5. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking dihydrocodeine (second 12-week period following the end of exposure): 1.03 (99% CI: 0.79-1.35)
	Codeine phosphate	1. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking codeine phosphate (4 week period up to and including the date of the prescription): 10.90 (99% CI: 9.33-12.74) 2. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking codeine phosphate (4-week period following the first prescription of a course of treatment): 1.61 (99% CI: 1.11-2.32) 3. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking codeine phosphate (remainder of exposed time): 1.33 (99% CI: 0.88-2.00) 4. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking codeine phosphate (12-week period following the end of exposure): 0.93 (99% CI: 0.69-1.24) 5. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking codeine phosphate (second 12-week period following the end of exposure): 0.85 (99% CI: 0.62-1.18)

Author (Year)	Drug(s)	Findings
	Morphine	1. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking morphine (4 week period up to and including the date of the prescription): 3.14 (99% CI: 1.60-6.15) 2. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking morphine (4-week period following the first prescription of a course of treatment): 1.16 (99% CI: 0.39-3.45) 3. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking morphine (remainder of exposed time): 0.87 (99% CI: 0.43-1.75) 4. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking morphine (12-week period following the end of exposure): 1.10 (99% CI: 0.49-2.47) 5. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking morphine (second 12-week period following the end of exposure): 1.42 (99% CI: 0.63-3.16)
	Opioids (All)	1. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking opioids (4 week period up to and including the date of the prescription): 10.90 (99% CI: 9.96-11.93) 2. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking opioids (4-week period following the first prescription of a course of treatment): 1.70 (99% CI: 1.39-2.08) 3. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking opioids (remainder of exposed time): 1.29 (99% CI: 1.08-1.54) 4. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking opioids (12-week period following the end of exposure): 1.02 (99% CI: 0.87-1.20) 5. Incident rate ratio (IRR) for involvement in a motor vehicle crash while taking opioids (second 12-week period following the end of exposure): 0.90 (99% CI: 0.75-1.08)
		1. Risk (odds ratio) for being involved in a motor vehicle crash while taking opioids (29-56 days before motor vehicle crash): 1.22 (99% CI: 0.94-1.59) 2. Risk (odds ratio) for being involved in a motor vehicle crash while taking opioids (57-84 days before motor vehicle crash): 1.46 (99% CI: 1.12-1.91) 3. Risk (odds ratio) for being involved in a motor vehicle crash while taking opioids (85-112 days before motor vehicle crash): 1.25 (99% CI: 0.97-1.62) 4. Risk (odds ratio) for being involved in a motor vehicle crash while taking opioids (113-140 days before motor vehicle crash): 1.45 (99% CI: 1.11-1.90) 5. Risk (odds ratio) for being involved in a motor vehicle crash while taking opioids (141-168 days before motor vehicle crash): 1.44 (99% CI: 1.11-1.85)
Gomes et al. (2013) [13]	Codeine, Morphine sulfate, Oxycodone or Hydromorphone Hydrochloride, and transdermal Fentanyl patches	1. Risk (adjusted odds ratio) of road trauma among new users taking any dose above very low compared to very low opioid doses (< 20 MEQ): 1.33 (CI: 0.84-2.12)

Author (Year)	Drug(s)	Findings
Nilsen et al. (2011) [30]	Codeine	1. Regression analyses (not provided) showed no influence from daily codeine dose on reaction time 2. Reaction time rural test (chronic pain patients without opioids vs. those using opioids): Difference=0.02, p=0.53 3. Reaction time urban test (chronic pain patients without opioids vs. those using opioids): Difference=0.00, p=0.98 4. Missed reactions urban test (chronic pain patients without opioids vs. those using opioids): Incident rate ratio=1.14, p=0.19
Prosser et al. (2009) [31]	Long-Term Methadone	1. Continuous Performance Task (CPT) Correct Hits (MMT/PA/COM): Mean score: 89.9, 118.62, 141.57; p = 0.001 2. Signal detection hit rate (correct response) (MMT/PA/COM): Mean score: 0.581, 0.785, 0.944; Post hoc: COMs>PAs >MMTs; p < .001 3. Signal detection false alarm rate (answering yes on a noise trial) (MMT/PA/COM): Mean score: 2.43×10^{-2}, 6.63×10^{-3}, 8.5×10^{-4}; Post hoc: MMTs > COMs; MMTs > PAs; p < .001 4. Signal detection d' (discriminate signal from noise) (MMT/PA/COM): Mean score: 2.53, 3.66, 4.98; Post hoc: COMs>PAs >MMTs; p < .001
Ravera & De Gier (2010) [16]	Opioids	1. Risk (odds ratio) for drivers being in a road traffic accident while taking opioids (new users): 1.34 (CI: 0.5-3.62) 2. Risk (odds ratio) for drivers being in a road traffic accident while taking opioids (chronic users): 1.13 (CI: 0.68-1.88)
Schumacher et al. (2011a) [32]	Stable oxycodone, oxycodone combined with Naloxone, hydromorphone, morphine, fentanyl, buprenorphine	1. Percent passing 5 VTS (Vienna Test System: above 16th percentile) tests: Patients=8%; Sober controls= 33%. Passing performance on 12 test variables (patients/sober controls): F=7.64, p< .05, controls>patients 2. Compared sum scores (z-transformed values) of all test variables (patients/sober controls): F=14.983, p<0.05, controls>patients 3. 1-sided t-test (patients/sober controls) on DT (Determination Test): p<.01, patients<controls 4. 1-sided t-test (patients/sober controls) on COG (measures attention reaction time): p=0.07 5. 1-sided t-test (patients/sober controls) on TAVTMB (Adaptive Tachistoscopic Traffic Perception Test), number of traffic situations without errors: p<.01, controls>patients 6. 1-sided t-test (patients/sober controls) on LVT (Visual Pursuit Test) number of correct answers in limited time frame: p<.01, controls>patients 7. 1-sided t-test (patients/sober controls) on RT (Reaction Test) average reaction time: p<.05, controls<patients 8. 1-sided t-test (patients/sober controls) on 2-HAND (Two Hand Coordination Test), average time needed to pass the track: p<.05, controls<patients 9. 1-sided t-test (patients/sober controls) on VIGIL (Vigilance Test; patients/controls; one-sided test), total number of correct reactions: p=0.41 10. 1-sided t-test (patients/sober controls) on WRBTV (Vienna Risk Taking Test Traffic), average time distance: p<.01, controls>patients

Author (Year)	Drug(s)	Findings
Schumacher et al. (2011b) [33]	Stable oxycodone, oxycodone combined with Naloxone, hydromorphone, morphine, fentanyl, buprenorphine	1. ANOVA for driving performance (patients/sober controls) on SDLP (standard deviation of lateral position): p=0.166 2. ANOVA for driving performance (patients/sober controls) on maintaining speed: p=0.09 3. ANOVA for driving performance (patients/sober controls) on TSA (time to speed adaptation): p=0.09 4. ANOVA for driving performance (patients/sober controls) on gain (amount of overshoot when lead car speeds up): p=0.89 5. ANOVA for driving performance (patients/sober controls) on coherence (correspondence between speed signals): p=0.24 6. ANOVA for driving performance (patients/sober controls) on BRT (brake reaction time): p=0.32 7. ANOVA for subjective measures (patients/sober controls) on performance: p=0.35 (road tracking) and p=0.30 (following) 8. ANOVA for subjective measures (patients/sober controls) on KSS (sleepiness): p=0.02 (road tracking, patients less sleepy) and p=0.06 (following) 9. ANOVA for subjective measures (patients/sober controls) on effort p=0.21 (road tracking) and p=0.09 (following)
Sobanksi et al. (2008) [45]	Methylphenidate (baseline vs. 6 weeks treatment)	1. ANOVA for LL5 (visual orientation, total answers) control group vs. medication group: F=5.47, p<.0.05 (medication higher) 2. ANOVA for Q1 (sustained attention, total answers) control group vs. medication group: F=1.14, n.s. 3. ANOVA for TT15 (track of complex situations) control group vs. medication group: F=1.92, p<0.01 (medication higher) 4. ANOVA for RST3 (reaction behavior phase 1, correct) control group vs. medication group: F=1.25, n.s. 5. ANOVA for RST3 (reaction behavior phase 2, correct) control group vs. medication group: F=5.09, p<0.05 (medication higher) 6. ANOVA for RST3 (reaction behavior phase 3, correct) control group vs. medication group: F=0.73, n.s.

Table 29 show findings pertaining to Q3 from systematic literature reviews.

Table 29: Systematic Reviews that Address Q3

Author (Year)	Study Objective	Databases Searched	Drug(s) (Dose)	Findings and Conclusions
ECRI & MANILA (2006) [19]	Investigate the relationship between licit use of Schedule II drugs and CMV crashes	Medline, PubMed (pre-Medline), EMBASE, PsycINFO, CINAHL, TRIS, and the Cochrane library (thru 2006)	Opioids and Stimulants	**Conclusions:** No conclusions concerning the relationship between drug interactions and crash risk can be drawn. **Findings:** Did not find any data to address this relationship
			Opioids	**Conclusions:** First-time administration of a single therapeutic dose to opioid-naïve individuals has a deleterious effect on psychomotor and high-level (but not low-level) cognitive function (Strength of Evidence: Moderate). Not enough data to draw conclusions on other effects or chronic use. **Findings:** Limited findings to address chronic vs. stable usage
			Stimulants	**Conclusions:** Administration of a single therapeutic dose to stimulant-naïve individuals does not appear to have a deleterious impact on cognitive or psychomotor function (Strength of Evidence: Weak). **Findings:** Limited findings to address chronic vs. stable usage
			Opioids and Stimulants	**Conclusions:** Limited data about the effect of combining a Schedule II drug with another drug on driving ability and cognitive or psychomotor function, mood or behavior. **Findings:** Limited findings

Author (Year)	Study Objective	Databases Searched	Drug(s) (Dose)	Findings and Conclusions
Fishbain et al. (2003) [20]	To determine what evidence, if any, exists for or against opioid-related driving impairment in opioid-dependent/tolerant patients	Medline, Psychological Abstracts, Science Citation Index, and the National Library of Medicine Physician Data Query (PDQ) (1966-2001)	Opioids (various)	**Conclusions:** No evidence for higher accident risk. About a third of 23 identified studies found that patients on stable opioid doses had some impairment of psychomotor abilities. **Findings:** 1. Strong, consistent evidence for no greater incidence of motor vehicle violations/motor vehicle accidents versus comparable controls of opioid-maintained patients 2. Moderate, generally consistent evidence for no impairment of psychomotor abilities of opioid-maintained patients 3. Inconclusive evidence on multiple studies for no impairment on cognitive function of opioid-maintained patients 4. Strong consistent evidence on multiple studies for no impairment of psychomotor abilities immediately after being given doses of opioids 5. Consistent evidence for no impairment as measured in driving simulators for opioid-maintained patients
Kurita et al. (2008) [47]	To better understand the effects of opioids on the cognitive function in cancer pain patients	PubMed, EMBASE, PsycInfo, CINAHL, and Lilacs (1989-2005)	Opioids (various)	**Conclusions:** Majority of the studies (evidence base is small) showed minor cognitive deficits associated with long-term opioid use. Cognitive impairment was also associated with dose increase and supplemental doses of short-acting opioids. **Findings:** Review of relevant studies found that a majority show minor cognitive deficits in long-term opioid patients
Raes et al. (2008) [23]	Investigate evidence from experimental and field studies of the relationship between drug use, driving impairment, and traffic accidents	ISI Web of Science, PubMed (Medline), Psychinfo and Transport (not provded)	Opioids	**Conclusions/Findings:** Patients on long-term opioid therapy exhibit some impairment of psychomotor and cognitive performance.
			Amphetamines	**Conclusions/Findings:** Chronic use of amphetamines causes negative effects on cognitive and psychomotor skills, which last longer than the period of intoxication and are sometimes correlated with the severity or duration of use.

Author (Year)	Study Objective	Databases Searched	Drug(s) (Dose)	Findings and Conclusions
Strand et al. (2011) [48]	Review experimental studies on drugs and driving/tasks related to driving for opioids, narcoanalgesics	MEDLINE, EMBASE, and PsycINFO (thru 2007)	Morphine	**Conclusions:** Some evidence of impairment among those chronically treated, but this may be because of pain itself. **Findings:** 1. Majority of studies found impaired psychomotor ability in pain patients treated chronically with morphine compared to healthy controls 2. No clear differences in psychomotor performance, cognitive abilities, or driving (simulator, road) performance compared to patients with similar diseases
Strand et al. (2013) [24]	Review treatment with methadone related to effects on cognitive and psychomotor functions of relevance to driving in experimental studies	MEDLINE, EMBASE, and PsycINFO (thru 2010)	Methadone (2-400 mg)	**Conclusions:** Recent studies have found an increased risk of traffic accident for methadone-maintained patients. Majority studies show cognitive and psychomotor impairments in methadone-maintained patients **Findings:** 1. Two recent and large studies found an increased risk of traffic accident involvement and an increased risk of being responsible for an accident when exposed to methadone 2. In 22/28 studies, some tests revealed significant impairment; in all, impairment was observed in 129 out of 407 tests performed; 10 tests reported some improvement

Author (Year)	Study Objective	Databases Searched	Drug(s) (Dose)	Findings and Conclusions
Wilhelmi & Cohen (2012) [25]	Investigate psychomotor effects of opioids	PubMed (not provided)	Morphine (30-60 mg); Hydrocodone/Acetaminophen (50-20 mg/500-1000 mg); Oxycodone (10-30 mg); Acetaminophen (1000 mg)	**Conclusions:** Review of relevant studies found that a majority show no difference in motor vehicle accidents or motor vehicle violations for stable use opioid patients. Current research has established two groups of opioid users: those who have recently begun opioid therapy or who have recently increased their dosage and are likely to demonstrate psychomotor impairment; and chronic users who do not appear to demonstrate significant psychomotor impairment. **Findings:** 1. Seven of eight studies found no increase in the number of motor vehicle violations or motor vehicle accidents compared with age-matched controls 2. Majority of studies show no psychomotor impairment for stable opioid use patients; 16 of 23 studies supported the conclusion that no psychomotor impairment exists in patients on stable opioid dosages 3. Majority of studies show cognitive impairment in stable use opioid patients; 5 of 11 studies that examined whether cognitive function was impaired found no impairment 4. Majority of studies show no impairment in driving simulator tasks or on-road driving in chronic opioid therapy patients; 2 of the 3 studies demonstrated that patients performed as well as their control-group counterparts

Findings

Findings are presented for drug interactions and for stable use. Findings from original research studies appear first, followed by relevant findings from systematic reviews.

Drug interactions

There was limited evidence on drug interactions, consisting of four original research studies.

Two studies looked at the effects of opiates combined with paracetamol. Verster & Roth [38] compared the effects of oxycodone/paracetamol at two doses (5/325mg and 10/650 mg) to placebo. They found some significant differences. This is similar to the finding of Zacny & Lichtor [36] who looked at the effects of 20 mg of oxycodone alone. Amato et al. [26] found no significant differences between three doses of codeine/paracetamol and a placebo on a variety of tests. This is similar to Nilsen et al.'s [30] finding that codeine does not impair patients with chronic pain over and above the impairment of chronic pain itself.

Gibson et al. [11] found the risk of motor vehicle crash is increased by the use of compound analgesic preparations containing acetaminophen and an opioid. The use of acetaminophen/opioid analgesic preparations is associated with an increased risk of motor vehicle crash in the first four weeks of treatment (IRR=2.06, 99% CI: 1.84-2.32), which returns to baseline levels after treatment ends. This is slightly higher than the risk for opioids alone (IRR=1.70, 99% CI: 1.39-2.08), but follows a similar pattern, although the difference is not significant.

Bachs et al. [1] looked at the risk of injury for drivers fulfilling a prescription for codeine. While this risk was generally elevated (across a variety of conditions) it dropped to non-significant when co-prescriptions were excluded.

The only identified systematic review to address this question (ECRI & MANILA [19]) drew no conclusions due to a lack of data.

Stable use: original research

Nine original research studies investigated stable use. Six of these studies simply report findings from subjects who have used the study drug for an extended period of time.

Three of these studies found that stable use patients do not have an elevated risk. For example, Nilsen et al. [30] found no difference in reaction time between chronic pain patients using codeine and chronic pain patients who are not using codeine. Likewise, Gaertner et al. [28] found that patients on controlled release oxycodone did not deviate

from controls relative to psychomotor performance, although this finding was only using a weaker statistical test. And, Sobanksi et al. [45] found improvement when investigating the effects of methylphenidate on adults with ADHD after six weeks of treatment: The medication group performed better on three tasks, including visual orientation ($p<0.05$), tracking complex situations ($p<0.01$), and reaction behaviors ($p<0.05$).

Two studies collectively show mixed results. Schumacher et al. conducted studies comparing patients on stable opioid analgesics to healthy controls. Patients with chronic pain treated with stable doses of opioid analgesics show impairment in driving related skills compared to healthy controls (Schumacher et al. [33]). However, a similar study design by the same authors comparing patients with sober controls on actual driving did not find any differences (Schumacher et al. [32]).

One study showed impairment, although the impairment is not necessarily from the study drug, since the underlying medical condition causes impairment. Prosser et al. [31] compared methadone maintained patients to controls in protracted abstinence and healthy controls. Subjects receiving methadone replacement therapy have worse performance than do subjects in protracted abstinence ($p<0.01$), and both do worse than healthy controls.

Two studies investigate specifically how new drug users fare. Gomes et al. [13] found the risk for new opioid users of road trauma was not significant (adjusted OR=1.33 (CI: 0.84-2.12)), even though the overall risk was elevated. Ravera & De Gier [16] found the risk for drivers of being in a road traffic accident while taking opioids was higher for new users (OR=1.34 (CI: 0.5-3.62)) than for chronic users (OR=1.13 (CI: 0.68-1.88)), although the difference is not significant and neither risk is significantly elevated.

Finally, Gibson et al. [11] investigates the risk of being in a motor crash over time for three specific opioids and for opioids overall. All follow the pattern of the risk being initially elevated as drug use begins and then decreasing to non-significant when drug use ends, although the timing varies. Both dihydrocodeine and codeine phosphate remain elevated through four weeks from date of prescription; morphine is elevated only up to the date of prescription, and opioids overall are elevated through the entire exposure time.

Stable use: systematic reviews

Seven systematic reviews investigate stable use. Most findings relate to opioids, although a few investigate stimulants.

ECRI & MANILA [19] concluded that first-time opioid use has an impairing effect.

Raes et al. [23] found that patients on long-term opioid therapy exhibit some impairment of psychomotor and cognitive performance. Kurita et al. [47] also found that a majority of studies show minor cognitive deficits in long-term opioid patients. However, Wilhelmi & Cohen [25] found that a majority of relevant studies show no difference in motor vehicle accidents or motor vehicle violations for stable use opioid patients; they found no evidence of psychomotor impairment; cognitive impairment; or impairment on driver simulator tasks. Fishbain [20] reached a similar conclusion that for opioid-maintained patients there is no greater incidence of motor vehicle violations/motor vehicle accidents; no impairment of psychomotor abilities; and no impairment in driver simulators.

Strand et al. [48] found that a majority of studies found impaired psychomotor ability in pain patients treated chronically with morphine, but there is no clear differences in psychomotor performance, cognitive abilities, or driving (simulator, road) performance compared to patients with similar diseases.

Strand et al. [24] found that recent studies have found an increased risk of traffic accident for methadone-maintained patients. The majority of studies show cognitive and psychomotor impairments in methadone-maintained patients, especially recent studies.

Related to stimulants, ECRI & MANILA [19] concluded that first time stimulant use likely does not have an impairing effect. However, Raes et al. [23] found that chronic use of amphetamines causes negative effects on cognitive and psychomotor skills, which last longer than the period of intoxication and are sometimes correlated with the severity or duration of use.

Conclusions

The evidence pertaining to whether Schedule II opioids and stimulants interact with other Schedule II or prescription medications is unacceptably weak. Limited data investigates the question of interactions, and what data do exist, conflict. Findings are likely drug and dose specific, and an insufficient evidence base exists at this time to adequately address the question.

There is moderate evidence that stable use of Schedule II opioids is associated with reduced negative impacts. Consistent data suggest that the negative impacts of opioids on driving and driving related skills diminish over time when doses remain stable. This is not the case for positive impacts, such as those that may be associated with

methadone maintenance treatments. However, negative effects of opioids may still remain, even in chronic users.

The evidence pertaining to whether chronic use of stimulants impacts driving or driving related skills is unacceptably weak. A limited evidence base makes it difficult to draw conclusions on this topic.

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Appendixes

A. Search Summaries

A unique set of keyword combinations was used for each search topic to identify potential studies of interest. These keyword combinations varied slightly for each database, to reflect its organizational structure.

The search terms used for PubMed are provided here for reference:

- **For Q1a:** (((((("opioid" OR "opioids" OR "opiate" OR "opiates" OR "opium" OR "pain medicine" OR "narcotic analgesic" OR "narcotic analgesics" OR "pain reliever" OR "stimulant" OR "stimulants" OR "dextroamphetamine" OR "methamphetamine" OR "methylamphetamine" OR "amphetamine" OR "methylphenidate" OR "pemoline" OR "phenmetrazine" OR "lisdexamfetamine" OR "methylamine")))))) AND ("trucking" OR "commercial motor vehicle" OR "CMV" OR "commercial driving" OR "driving" OR "auto" OR "automobile" OR "driver" OR "motor vehicle"))) AND ("traffic accident" OR "automobile accident" OR "motor vehicle accident" OR "traffic crash" OR "automobile crash" OR "motor vehicle crash" OR "traffic related injury" OR "traffic injury" OR "automobile injury" OR "motor vehicle injury")))
- **For Q1a/Q2:** (("opioid" OR "opioids" OR "opiate" OR "opiates" OR "opium" OR "pain medicine" OR "narcotic analgesic" OR "narcotic analgesics" OR "pain reliever" OR "stimulant" OR "stimulants" OR "dextroamphetamine" OR "methamphetamine" OR "methylamphetamine" OR "amphetamine" OR "methylphenidate" OR "pemoline" OR "phenmetrazine" OR "lisdexamfetamine" OR "methylamine"))) AND (("trucking" OR "commercial motor vehicle" OR "CMV" OR "commercial driving" OR "driving" OR "auto" OR "automobile" OR "driver" OR "motor vehicle"))) AND (("traffic accident" OR "automobile accident" OR "motor vehicle accident" OR "traffic crash" OR "automobile crash" OR "motor vehicle crash" OR "traffic related injury" OR "traffic injury" OR "automobile injury" OR "motor vehicle injury"))) AND (("serum" OR "serum concentration" OR "plasma concentration" OR "drug concentration" OR "blood concentration" OR "maximum concentration" OR "Cmax" OR "metabolism" OR "pharmacokinetic"))
- **For Q1a/Q3:** (((((("opioid" OR "opioids" OR "opiate" OR "opiates" OR "opium" OR "pain medicine" OR "narcotic analgesic" OR "narcotic analgesics" OR "pain reliever" OR "stimulant" OR "stimulants" OR "dextroamphetamine" OR "methamphetamine" OR "methylamphetamine" OR "amphetamine" OR "methylphenidate" OR "pemoline" OR "phenmetrazine" OR "lisdexamfetamine"

OR "methylamine"))))) AND ("trucking" OR "commercial motor vehicle" OR "CMV" OR "commercial driving" OR "driving" OR "auto" OR "automobile" OR "driver" OR "motor vehicle"))) AND ("traffic accident" OR "automobile accident" OR "motor vehicle accident" OR "traffic crash" OR "automobile crash" OR "motor vehicle crash" OR "traffic related injury" OR "traffic injury" OR "automobile injury" OR "motor vehicle injury"))) AND (("drug interaction" OR "drug interactions" OR "drug-drug interaction" OR "drug-drug interactions" OR "adverse reaction" OR "adverse reactions" OR "complication" OR "complications" OR "side effect" OR "side effects"))

- **For Q1b:** ((((("opioid" OR "opioids" OR "opiate" OR "opiates" OR "opium" OR "pain medicine" OR "narcotic analgesic" OR "narcotic analgesics" OR "pain reliever" OR "stimulant" OR "stimulants" OR "dextroamphetamine" OR "methamphetamine" OR "methylamphetamine" OR "amphetamine" OR "methylphenidate" OR "pemoline" OR "phenmetrazine" OR "lisdexamfetamine" OR "methylamine"))) AND (("trucking" OR "commercial motor vehicle" OR "CMV" OR "commercial driving" OR "driving" OR "auto" OR "automobile" OR "driver" OR "motor vehicle"))) AND (("potentially driver-impairing" OR "PDI" OR "drug driving" OR "drugged driving" OR "impaired driving" OR "drug-impaired driving" OR "drug impairment" OR "driving ability" OR "driving performance" OR "simulated driving" OR "driver simulator" OR "fitness to drive" OR "driver fitness" OR "psychomotor performance" OR "psychomotor effects" OR "cognitive function" OR "cognitive functioning" OR "cognition" OR "physiologic reaction" OR "vision" OR "motor function" OR "Psychomotor Vigilance Tasks" OR "Psychomotor Vigilance Task" OR "PVT"))))
- **For Q1b/Q2:** ((((((("opioid" OR "opioids" OR "opiate" OR "opiates" OR "opium" OR "pain medicine" OR "narcotic analgesic" OR "narcotic analgesics" OR "pain reliever" OR "stimulant" OR "stimulants" OR "dextroamphetamine" OR "methamphetamine" OR "methylamphetamine" OR "amphetamine" OR "methylphenidate" OR "pemoline" OR "phenmetrazine" OR "lisdexamfetamine" OR "methylamine"))) AND (("trucking" OR "commercial motor vehicle" OR "CMV" OR "commercial driving" OR "driving" OR "auto" OR "automobile" OR "driver" OR "motor vehicle"))) AND (("potentially driver-impairing" OR "PDI" OR "drug driving" OR "drugged driving" OR "impaired driving" OR "drug-impaired driving" OR "drug impairment" OR "driving ability" OR "driving performance" OR "simulated driving" OR "driver simulator" OR "fitness to drive" OR "driver fitness" OR "psychomotor performance" OR "psychomotor effects" OR "cognitive function" OR "cognitive functioning" OR "cognition" OR "physiologic reaction" OR "vision" OR "motor function" OR "Psychomotor Vigilance Tasks" OR "Psychomotor Vigilance Task" OR "PVT"))) AND (("serum" OR "serum concentration" OR "plasma concentration" OR "drug concentration"

OR "blood concentration" OR "maximum concentration" OR "Cmax" OR "metabolism" OR "pharmacokinetic"))))

- **For Q1b/Q3:** (((((("opioid" OR "opioids" OR "opiate" OR "opiates" OR "opium" OR "pain medicine" OR "narcotic analgesic" OR "narcotic analgesics" OR "pain reliever" OR "stimulant" OR "stimulants" OR "dextroamphetamine" OR "methamphetamine" OR "methylamphetamine" OR "amphetamine" OR "methylphenidate" OR "pemoline" OR "phenmetrazine" OR "lisdexamfetamine" OR "methylamine"))) AND (("trucking" OR "commercial motor vehicle" OR "CMV" OR "commercial driving" OR "driving" OR "auto" OR "automobile" OR "driver" OR "motor vehicle"))) AND (("potentially driver-impairing" OR "PDI" OR "drug driving" OR "drugged driving" OR "impaired driving" OR "drug-impaired driving" OR "drug impairment" OR "driving ability" OR "driving performance" OR "simulated driving" OR "driver simulator" OR "fitness to drive" OR "driver fitness" OR "psychomotor performance" OR "psychomotor effects" OR "cognitive function" OR "cognitive functioning" OR "cognition" OR "physiologic reaction" OR "vision" OR "motor function" OR "Psychomotor Vigilance Tasks" OR "Psychomotor Vigilance Task" OR "PVT"))) AND (("drug interaction" OR "drug interactions" OR "drug-drug interaction" OR "drug-drug interactions" OR "adverse reaction" OR "adverse reactions" OR "complication" OR "complications" OR "side effect" OR "side effects")))

B. Retrieval Criteria

These searches produced large numbers of search results. A member of our research team reviewed the title and abstract of each returned article. This information was reviewed against a set retrieval criteria that were defined a priori. If the article matched the criteria, it was entered into a reference database with a notation about which question it apparently applied to. Each article was obtained in full text (typically as a PDF file), and attached to the bibliographic information in the database.

The retrieval criteria were:

Retrieval Criteria for Key Question 1

- Article must be published in the English language.
- Article must be full-length and not a letter, editorial, news, comment, case report, review, note, abstract, or conference paper.
- Article must describe a study that enrolled 10 or more subjects over the age of 18.
- Article must describe a study on the licit use of prescribed Schedule II opioids or stimulants. If illicit use is included in the study, the effects of licit and illicit use must be separable. If drugs other than Schedule II opioids or stimulants are included in the study, the effects of opioids and/or stimulants must be separable.
- Article must describe a study that shows the relationship between licit use and risk of a crash (CMV or automobile) or on driver performance (including effects of cognitive or psychomotor functions).
- Study must be published after January 1, 2006.

Retrieval Criteria for Key Question 2

- Article must be published in the English language.
- Article must be full-length and not a letter, editorial, news, comment, case report, review, note, abstract, or conference paper.
- Article must describe a study that enrolled 10 or more subjects over the age of 18.
- Article must describe a study on the licit use of prescribed Schedule II opioids or stimulants. If illicit use is included in the study, the effects of licit and illicit use must be separable. If drugs other than Schedule II opioids or stimulants are included in the study, the effects of opioids and/or stimulants must be separable.
- Article must describe a study that shows the relationship between licit use and risk of a crash (CMV or automobile) or on driver performance (including effects of cognitive or psychomotor functions).
- Article must describe a study that addresses serum concentrations or metabolism or other pharmacokinetic parameters related to the drug.
- Study must be published after January 1, 2006.

Retrieval Criteria for Key Question 3

- Article must be published in the English language.
- Article must be full-length and not a letter, editorial, news, comment, case report, review, note, abstract, or conference paper.
- Article must describe a study that enrolled 10 or more subjects over the age of 18.
- Article must describe a study on the licit use of prescribed Schedule II opioids or stimulants. If illicit use is included in the study, the effects of licit and illicit use must be separable. If drugs other than Schedule II opioids or stimulants are included in the study, the effects of opioids and/or stimulants must be separable.
- Article must describe a study that shows the relationship between licit use and risk of a crash (CMV or automobile) or on driver performance (including effects of cognitive or psychomotor functions).
- Article must describe a study that addresses drug interactions between these drugs and other Schedule II or OTC medicines or it must address the effects of stable use of the drug.
- Study must be published after January 1, 2006.

C. Inclusion Criteria

Once all sources had been searched, the reference database was searched to eliminate duplicate articles. A researcher then reviewed each article, again against a set of exclusion and inclusion criteria. These a priori criteria, below, largely mirror the retrieval criteria, but this time the decision was made based on a review of the full-text of the article as opposed to the abstract only.

Inclusion Criteria for all Questions

- Article must be published in the English language.
- Article must be full-length and not a letter, editorial, news, comment, case report, review, note, abstract, or conference paper.
- Article must describe a study that enrolled 10 or more subjects.
- Most subjects must be over the age of 18 (but we will include studies that have some subjects under 18).
- Article must describe a study on the licit use of prescribed Schedule II opioids or stimulants (see list of drugs).
    - If illicit use is included in the study, the effects of licit and illicit use must be separable.
    - If drugs other than Schedule II opioids or stimulants are included in the study, the effects of Schedule II opioids and/or stimulants must be separable.
- Study must be published after January 1, 2006.
- If the same study is reported in multiple publications, the most complete publication will be the primary reference. Full-length studies will not be double counted.

In addition to these criteria, there are criteria specific to each research question.

Inclusion Criteria for Key Question 1a

- Article must describe a study that shows the relationship between licit use and risk of a crash (CMV or automobile) or auto related injury/fatality.
- Either original research on this topic (with 10 or more subjects) or a systematic review qualifies.

Inclusion Criteria for Key Question 1b

- Article must describe a study that shows the relationship between licit use and driver performance (including effects on cognitive or psychomotor functions; this includes driving simulators).

- Either original research on this topic (with 10 or more subjects) or a systematic review qualifies.

Inclusion Criteria for Key Question 2

- Article must describe a study that shows the relationship between licit use and risk of a crash (CMV or automobile) or on driver performance (including effects of cognitive or psychomotor functions). In other words, there should be data in it that qualify for Q1a or Q1b.
- Article must describe a study that addresses serum concentrations or metabolism or other pharmacokinetic parameters related to the drug.
- Either original research on this topic (with 10 or more subjects) or a systematic review qualifies.

Inclusion Criteria for Key Question 3

- Article must describe a study that shows the relationship between licit use and risk of a crash (CMV or automobile) or on driver performance (including effects of cognitive or psychomotor functions). In other words, there should be data in it that qualify for Q1a or Q1b.
- Article must describe a study that addresses drug interactions between these drugs and other Schedule II or over the counter (OTC) medicines or it must address the effects of stable use of the drug.
- Article must report either original research on this topic (with 10 or more subjects) or a systematic review of the scientific literature

Reviewers were instructed to check the drugs studied against a list of qualifying Schedule II opioids or stimulants.

D. Qualifying Schedule II Opioids and Stimulants

Opiates

- Alfentanil
- Alphaprodine
- Anileridine
- Bezitramide
- Bulk dextropropoxyphene (non-dosage forms)
- Carfentanil
- Codeine
- Concentrate of poppy straw (the crude extract of poppy straw in either liquid, solid or powder form which contains the phenanthrene alkaloids of the opium poppy)
- Dihydrocodeine
- Dihydroetorphine
- Diphenoxylate
- Ethylmorphine
- Etorphine hydrochloride
- Fentanyl
- Granulated opium
- Hydrocodone
- Hydromorphone
- Isomethadone
- Levo-alphacetylmethadol
- Levomethorphan
- Levorphanol
- Metazocine
- Methadone
- Metopon
- Morphine
- Opium extracts
- Opium fluid
- Opium poppy and poppy straw
- Oripavine
- Oxycodone
- Oxymorphone
- Pethidine (meperidine)
- Phenazocine
- Piminodine

- Powdered opium
- Racemethorphan
- Racemorphan
- Raw opium
- Remifentanil
- Sufentanil
- Tapentadol
- Thebaine
- Tincture of opium

Opiate intermediants

- Methadone intermediate: 4-cyano-2-dimethylamino-4,4-diphenyl butane
- Moramide intermediate: 2-methyl-3-morpholino-1,1-diphenylpropane-carboxylic acid
- Pethidine intermediate A: 4-cyano-1-methyl-4-phenylpiperidine
- Pethidine intermediate B, ethyl-4-phenylpiperidine-4-carboxylate
- Pethidine intermediate C, 1-methyl-4-phenylpiperidine-4-carboxylic acid

Stimulants

- Amphetamine, its salts, optical isomers, and salts of its optical isomers (Adderall)
- Coca, leaves and any salt, compound, derivative or preparation of coca leaves
- Cocaine, and its salts, isomers, derivatives and salts of isomers and derivatives
- Ecgonine, and its salts, isomers, derivatives and salts of isomers and derivatives
- Lisdexamfetamine (Vyvanse), its salts, isomers, and salts of its isomers
- Methamphetamine, its salts, isomers, and salts of its isomers
- Methylphenidate (Ritalin, Concerta, etc.)
- Phenmetrazine and its salts