Evidence Report:
Licit Schedule II Drug Use and Commercial Motor Vehicle Driver Safety (Comprehensive Review)

Presented to

Federal Motor Carrier Safety Administration

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Prepared for

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This report is comprised of research conducted to analyze the impact of Licit Schedule II Drug Use on Commercial Motor Vehicle Driver Safety. Federal Motor Carrier Safety Administration considers evidence, expert recommendations, and other data, however, all proposed changes to current standards and guidance (guidelines) will be subject to public-notice-and-comment and regulatory processes.

Policy Statement

ECRI prepared this report under subcontract to MANILA Consulting Group, Inc., which holds prime Contract No. GS-10F-0177N/DTMC75-05-F-00062 with the Department of Transportation's Federal Motor Carrier Safety Administration. ECRI is an independent, nonprofit health services research agency and a Collaborating Center for Health Technology Assessment of the World Health Organization. ECRI has been designated an Evidence-based Practice Center (EPC) by the United States Agency for Healthcare Research and Quality. ECRI's mission is to provide information and technical assistance to the healthcare community worldwide to support safe and cost-effective patient care. The results of ECRI's research and experience are available through its publications, information systems, databases, technical assistance programs, laboratory services, seminars, and fellowships. The purpose of this evidence report is to provide information on the current state of knowledge on this topic. It is not intended as instruction for medical practice or for making decisions regarding individual patients.

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Executive Summary

Purpose of Evidence Report

Of all occupations in the United States, workers in the trucking industry experience the third-highest fatality rate, accounting for 12 percent of all worker deaths. About two-thirds of fatally injured truck workers were involved in highway crashes. According to statistics from the United States Department of Transportation for 2005, 137,144 crashes involved a large truck. Of these, 59,405 were crashes that resulted in an injury to at least one individual for a total of 89,681 injuries. In 2004,[1] 4,862 large trucks were involved in fatal crashes for a total of 5,190 fatalities. The purpose of this evidence report is to examine the relationship between the licit use of a Schedule II drug and the risk for a motor vehicle crash. To meet the aims of this evidence report, we addressed the following eight key questions:

Key Question 1: Does the licit use of a prescribed Schedule II drug increase the risk for a motor vehicle crash?

Key Question 2: Does the licit use of a prescribed Schedule II drug negatively impact indirect measures of driving ability?

Key Question 3: What is the correlation between the serum level of a Schedule II drug and the risk for a motor vehicle crash?

Key Question 4: What is the correlation between the serum level of a Schedule II drug and indirect measures of driving ability?

Key Question 5: Is there a relationship between the pharmacokinetics of a Schedule II drug and the risk for a motor vehicle crash?

Key Question 6: Is there a relationship between the pharmacokinetics of a Schedule II drug and indirect measures of driving ability?

Key Question 7: Are there common drug interactions that include a prescribed Schedule II drug that increase the risk for a motor vehicle crash?

Key Question 8: Are there common drug interactions that include a prescribed Schedule II drug that affect indirect measures of driving ability?

Identification of Evidence Bases

Separate evidence bases for each of the key questions addressed by this evidence report were constructed by performing a comprehensive search of the literature, examining the abstracts of identified studies to determine which articles would be retrieved, and selecting the actual articles that would be included in each evidence base.

A total of seven electronic databases (Medline, PubMed (pre-Medline), EMBASE, PsycINFO, CINAHL, TRIS, and the Cochrane library) were searched (through June 28, 2006). In addition, we examined the reference lists of all obtained articles with the aim of identifying relevant articles not identified by our electronic searches. Hand searches of

[1] Fatality data for 2005 were not available at the time of writing.

the "gray literature" were also performed. Admission of an article into an evidence base was determined by formal retrieval and inclusion criteria determined a priori.

Grading the Strength of Evidence

Our assessment of the quality of the evidence took into account the quality of the individual studies that comprise the evidence base for each key question. We also considered the interplay between the quality, quantity, robustness, and generalizability (to the specific target population of interest) of the overall body of evidence.

Analytic Methods

Meta-analysis of the data extracted from the studies meeting the inclusion criteria for this evidence report was not appropriate. Consequently, the conclusions of this report are based on the findings of a series of qualitative assessments of the available evidence.

Presentation of Findings

The strength-of-evidence ratings assigned to the findings presented in this report are defined in Table 1.

Table 1. Strength-of-Evidence Ratings for Qualitative and Quantitative Conclusions

Strength of Evidence	Interpretation
High	The estimate of treatment effect in the conclusion is stable. The magnitude of this estimate is highly unlikely to change substantially as a result of the publication of new evidence.
Moderate	The estimate of treatment effect in the conclusion is somewhat stable. A small chance exists that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI recommends regular monitoring of the relevant literature.
Low	The estimate of treatment effect in the conclusion is likely to be unstable. A reasonable chance exists that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI recommends frequent monitoring of the relevant literature.
Unstable	Estimates of the treatment effect are too unstable to allow a quantitative conclusion to be drawn at this time. ECRI recommends frequent monitoring of the relevant literature.

Findings

Specific findings of our assessment of the evidence that pertains to the eight key questions addressed in this evidence report are presented below.

Key Question #1: Does the licit use of a prescribed Schedule II drug increase the risk for a motor vehicle crash?

Whether a relationship exists between the licit use of a Schedule II drug and motor vehicle (any category) crash risk cannot be determined at the present time.

Although our searches identified and retrieved 49 potentially relevant articles, none met the inclusion criteria for this key question. The primary reason for exclusion was that studies combined crash data from licit and illicit Schedule II drug users (32 studies). Because illicit drug users do not use drugs in a manner that is compatible with a therapeutic regimen (the aim of a drug abuser is to use the drug to deliberately initiate a change in mental state, whereas the aim of a licit user is to treat a disorder), crash data

that include drug abusers cannot provide an answer to Key Question 1. The second reason for exclusion was that several studies were designed to examine the crash risk associated with a particular drug class that encompassed drugs spanning several drug schedules (eight studies). Not all opioids, stimulants, and depressants are Schedule II drugs, and studies that evaluated crash risk by drug class did not stratify crash risk data by United States Drug Enforcement Agency drug schedule.

Key Question #2: Does the licit use of a prescribed Schedule II drug negatively impact indirect measures of driving ability?

General Finding

1. **A paucity of data from studies that enrolled commercial motor vehicle (CMV) drivers precludes direct determination of whether the driving ability (as measured using a simulator or on a specific test circuit), cognitive and psychomotor function, or the mood and behavior of CMV drivers are adversely affected by the licit use of any Schedule II opioids.**

   Two included studies enrolled individuals who could potentially be considered CMV drivers. Both studies recruited individuals whom the study investigators termed "professional drivers". However, the articles describing these studies are unclear on how the study investigators defined a "professional driver". Consequently, the possibility remains that none, or only a small proportion, of the enrollees in these two studies actually drove large trucks or buses.

Findings Specific to Licit Schedule II Opioid Use

1. **A paucity of high-quality data makes it impossible to draw an evidence-based conclusion about whether first-time administration of a Schedule II opioid has a deleterious effect on driving ability.**

   A single, small, low-quality study evaluated the effects of a single 50 mg oral dose of codeine on driving ability as measured using a driving simulator in opioid-naïve healthy individuals. This study found that codeine had a significant deleterious effect on driving ability. Because this study is not of high quality, however, and its findings have not yet been replicated, an evidence-based conclusion cannot be drawn at the present time.

2. **A paucity of high-quality data makes it impossible to draw an evidence-based conclusion on whether licit Schedule II opioid use has a deleterious effect on driving ability among individuals who have used long-term stable doses of the drug for a legitimate medical reason.**

   A single, small, low-quality study evaluated the effects of stable doses of various opioids on the driving ability of individuals with chronic pain. No evidence of a driving ability deficit was observed in long-term opioid users on either a community driving course or an obstacle course. Because this study is not of high quality and its findings have not yet been replicated, an evidence-based conclusion cannot be drawn at the present time.

3. **First-time administration of a single therapeutic dose of a Schedule II opioid to opioid-naïve individuals has a deleterious effect on psychomotor and high-level (but not low-level) cognitive function (Strength of Evidence: Moderate).**

   Six small, but otherwise high-quality studies, assessed the effects of the administration of an opioid on some measures of cognitive (high-level) and psychomotor function among opioid-naïve healthy individuals. Four of the six studies found that psychomotor and high-level cognitive function were adversely affected by a single dose of an opioid (morphine, alfentanil, meperidine, or fentanyl). The remaining two studies, both of which evaluated the effects of a single dose of codeine (30 to 100 mg), found no such drug effect. Whether the inconsistency in the findings of the six studies included in this assessment is a consequence of differences in the drugs themselves, dosage, measurement timing, the sensitivity of the psychometric instruments used to evaluate cognitive and psychomotor function, the size of the included studies, or the characteristics of the individuals enrolled in the studies cannot be determined at this time.

4. **Owing to a paucity of consistent data from high-quality trials, it is not possible at the present time to draw an evidence-based conclusion on whether chronic (>seven days) use of a Schedule II opioid has a deleterious impact on cognitive or psychomotor function.**

   Five low-quality studies assessed the effects of the long-term administration of an opioid on cognitive and psychomotor function among individuals with chronic pain. Three of the five included studies did not observe any detrimental effects of opioids on cognitive or psychomotor function. Two studies, however, provide limited evidence supporting the contention that the long-term use of a Schedule II opioid (transdermal fentanyl) may have a deleterious impact on cognitive and psychomotor function.

   None of the included studies in the evidence base considered here were designed as non-inferiority or equivalency studies. That is, they were not designed to test the hypothesis that the administration of therapeutic doses of an opioid does not have a deleterious impact on outcome. Rather, the included studies were designed to test the hypothesis that the administration of an opioid will have a deleterious impact on outcome. Failure to disprove the null hypothesis (not observing a treatment effect) by studies that use this design cannot be construed as providing evidence of no drug effect. Evidence from such studies, even when consistently observed by several independent studies can, at best, be considered suggestive of no treatment effect.

5. **A lack of data from studies in which a Schedule II opioid was administered to opioid-naïve individuals makes it impossible to determine whether first-time administration of an opioid has a detrimental effect on mood or behavior.**

   No included studies evaluated the effects of opioids on mood or behavior in opioid-naïve individuals.

6. **Currently available data do not provide evidence to support the contention that stable (no change in dose in the previous seven days) therapeutic doses of a Schedule II opioid (morphine) have a detrimental effect on mood or behavior (Strength of Evidence: Weak).**

Two small, low-quality studies examined the effects of an opioid on mood or behavior among individuals with chronic pain. Neither study provided any evidence to support the contention that long-term use of morphine for a licit purpose has a negative impact on mood or behavior.

As was the case above, neither included study was designed as a non-inferiority or equivalency study (designed to test the hypothesis that the administration of therapeutic doses of an opioid does not have a deleterious impact on outcome). Consequently, the finding of no evidence of a deleterious effect cannot be interpreted as providing evidence of no effect.

Findings Specific to Licit Schedule II Stimulant Use

1. **A lack of data precludes determination of whether the licit long-term use of a Schedule II stimulant for the treatment of a legitimate medical condition has a detrimental effect on driving ability (as measured using a simulator or on a specific test circuit), cognitive and psychomotor function, or mood and behavior such that the risk for a motor vehicle crash is increased.**

   No included studies evaluated the effects of the long-term licit use of a stimulant on any of the outcomes relevant to Key Question 2.

2. **Owing to a paucity of consistent data, it is not possible to draw an evidence-based conclusion about whether administration of therapeutic doses of a Schedule II stimulant to stimulant-naïve individuals has a detrimental impact on driving ability.**

   Two high-quality studies assessed the effects of Schedule II stimulants (dextroamphetamine and methylphenidate) on simulated driving ability. The findings of these two studies were not consistent. One study found that a single dose of dextroamphetamine has a deleterious impact on daytime (but not nighttime) simulated driving in stimulant-naïve individuals. The other study did not observe any deleterious effects on simulated driving ability that could be associated with methylphenidate (10 or 20 mg) when given to individuals with attention deficit hyperactivity disorder. Whether these differences in findings are the consequence of differences in the drugs tested, dosage, measurement timing, sensitivity of the driving simulators used to evaluate driving ability, size of the included studies, or characteristics of the individuals enrolled in the studies cannot be determined at this time.

3. **Administration of a single therapeutic dose of a Schedule II stimulant (dextroamphetamine or methylphenidate) to stimulant-naïve individuals does not appear to have a deleterious impact on cognitive or psychomotor function (Strength of Evidence: Weak).**

   Five moderate- to high-quality studies presented data on the acute effects of stimulants on cognitive and psychomotor function. None of the studies found that the administration of a therapeutic dose of a Schedule II stimulant had a deleterious impact on cognitive or psychomotor function. Despite the fact that the overall quality of the evidence base underpinning this conclusion was high, and the data from all five studies are qualitatively consistent and robust, we refrain from assigning a strength-

of-evidence rating of strong to this conclusion. This is because none of the included studies were non-inferiority or equivalency studies (see the discussion above: Conclusion 4 of the opioids section).

4. **Administration of a single therapeutic dose of a Schedule II stimulant (dextroamphetamine or methylphenidate) to stimulant-naïve individuals does not appear to have a deleterious impact on mood or behavior in a manner that would be considered detrimental to motor vehicle safety (Strength of Evidence: Weak).**

   Three high-quality studies presented data on the acute effects of a stimulant on mood and behavior. None of these studies found that stimulants had a deleterious effect on mood or behavior. In fact, data from the three studies suggest that some of the effects of the stimulants on mood and behavior were positive (e.g., improved focus). Despite the fact that the studies from which these data originated were of high quality, the findings should be viewed with caution. This is because mood and behavior data from two of the three studies included were based on test subject self-perception. Individuals' internal perception of their own behavior while under the influence of a drug cannot be considered a good indicator of their actual demeanor. Data from the third study are equally suspect because they were based on a rather informal description of the behavior of the test subjects. To reflect our concern about the potential mischaracterizations of the true mood and behavior states of the individuals enrolled in the included studies, we have downgraded the strength-of-evidence rating from High to Weak.

Findings Specific to Licit Schedule II Depressant Use

1. **A lack of data makes it impossible to determine whether the licit long-term use of a Schedule II depressant for the treatment of a legitimate medical condition has a detrimental effect on driving ability (as measured using a simulator or on a specific test circuit), cognitive and psychomotor function, or mood and behavior such that the risk for a motor vehicle crash is increased.**

   No included studies evaluated the effects of the long-term licit use of a Schedule II depressant on any of the outcomes relevant to Key Question 2.

2. **A paucity of data makes it impossible to draw an evidence-based conclusion on whether the administration of therapeutic doses of a Schedule II depressant to a depressant-naïve individual has a detrimental impact on driving ability.**

   One included moderate-quality study evaluated the effects of repeated doses (five doses over 36 hours) of a Schedule II depressant (amylobarbitone) on driving ability as measured by a series of low-speed vehicle handling tests. Test subjects were all young, healthy individuals. The results of the study suggest that a therapeutic dose of amylobarbitone, when taken over the preceding 36-hour period by healthy individuals, has a detrimental impact on driving ability. Because this study is not of high quality, however, and its findings have not yet been replicated, an evidence-based conclusion cannot be drawn at the present time.

3. **Therapeutic doses of Schedule II depressants (secobarbital or pentobarbital) appear to have a deleterious impact on cognitive and psychomotor function (Strength of Evidence: Weak).**

   Two moderate-quality studies consistently found that cognitive and psychomotor functions were impaired following the administration of a single dose of a Schedule II depressant (secobarbital or pentobarbital). Whether the results of these two studies can be generalized to other depressants in the same class (barbiturates) cannot be determined.

4. **A paucity of consistent data from high-quality trials makes it impossible to draw an evidence-based conclusion about whether the deleterious effects of Schedule II depressants continue to affect performance the morning after administration of a therapeutic dose.**

   Because one of the primary medical indications for a Schedule II depressant is insomnia, determining whether the adverse effects the drug has on cognitive or psychomotor function can be observed the morning after administration of the drug is important.

   Three studies evaluated the effects of a single dose of barbiturate the morning after its administration. The results of these studies were not consistent with one another. One moderate-quality study did not observe any reduction in cognitive or psychomotor function the morning after administration of a single 100 mg dose of amylobarbitone. However, the remaining two studies (one administered a single 200 mg dose of amylobarbitone and the other administered a single 200 mg dose of a mix of secobarbital and amobarbital) found that cognitive and psychomotor function were impaired the day after administration of the drug. Whether this inconsistency in the findings of the three included studies is a consequence of differences in drug dosage, the sensitivity of the psychometric instruments used to evaluate cognitive and psychomotor function, the size of the included studies, or in the characteristics of the individuals enrolled in the studies cannot be determined at this time.

5. **A paucity of data makes it impossible to draw an evidence-based conclusion about whether the chronic administration of therapeutic doses of a Schedule II depressant has a detrimental impact on cognitive or psychomotor function.**

   A single high-quality study evaluated the effects of seven days of administration of a Schedule II depressant (amylobarbitone) on cognitive or psychomotor function. This study enrolled individuals with a clinical diagnosis of anxiety neurosis who had been admitted to the hospital for crisis intervention. The study found that chronic therapeutic doses of amylobarbitone (463 mg/day) had a deleterious effect on cognitive and psychomotor function. Of the nine relevant outcomes measured, two were significantly impaired. Whether these findings are the consequence of chance or are representative of a true drug effect is not clear. Replication studies performed with different patient populations and Schedule II depressants are required before evidence-based conclusions about the effects of long-term Schedule II depressant treatment can be drawn.

6. **The best evidence currently available does not support the contention that therapeutic doses of a Schedule II depressant (amylobarbitone) have a deleterious impact on mood or behavior that would be detrimental to motor vehicle safety when administered to depressant-naïve individuals.**

   Two high-quality studies evaluated the effects of acute administration of a Schedule II depressant (amylobarbitone) on the mood and behavior of healthy, depressant-naïve individuals. Whether the results of these two studies can be generalized to other depressants in the same class (barbiturates) cannot be determined.

***Key Question #3:* What is the correlation between the serum level of a Schedule II drug and the risk for a motor vehicle crash?**

1. **No conclusions from direct evidence on the relationship between the serum level of a Schedule II drug and motor vehicle (any category) crash risk can be drawn at the present time.**

   Although we retrieved 49 potentially relevant articles that described 49 unique studies, none was found to report on the relationship between the serum level of a Schedule II drug and motor vehicle crash risk. Consequently, no evidence base currently exists that can be used to answer this question.

***Key Question #4:* What is the correlation between the serum level of a Schedule II drug and indirect measures of driving ability?**

1. **A lack of evidence makes it impossible to draw evidence-based conclusions about the relationship between serum levels of Schedule II stimulants and depressants and any of the outcomes of interest (driving ability, cognitive or psychomotor function, and mood or behavior).**

   No study meeting the inclusion criteria for Key Question 4 evaluated a Schedule II stimulant or depressant.

2. **A lack of evidence makes it impossible to draw evidence-based conclusions about the relationship between serum levels of Schedule II opioids and driving ability and mood or behavior.**

   No study meeting the inclusion criteria for Key Question 4 investigated the relationship between the serum level of a Schedule II opioid and driving ability and mood or behavior.

3. **The magnitude of the 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).**

   Three moderate- to high-quality studies observed a relationship between serum levels of a Schedule II opioid (morphine) and some (but not all) measures of cognitive or psychomotor dysfunction. The measures that demonstrated the strongest relationship with drug serum level tended to be measures of higher order functioning.

4. **Measures of high-level cognitive or psychomotor function are inversely correlated with the serum level of Schedule II opioids (Strength of Evidence: Weak).**

   Two low-quality studies observed significant correlations between serum levels of a Schedule II opioid (fentanyl or morphine) and a number of high-level measures of cognitive or psychomotor function.

***Key Question #5:* Is there a relationship between the pharmacokinetics of a Schedule II drug and the risk for a motor vehicle crash?**

1. **No conclusions from direct evidence on the relationship between Schedule II drug pharmacokinetics and motor vehicle (any category) crash risk can be drawn at the present time.**

   Although we retrieved 11 potentially relevant articles that described 11 unique studies, none provided direct evidence pertaining to the relationship between crash risk and the Schedule II drug pharmacokinetics. Consequently, no evidence base currently exists that can be used to answer this question.

***Key Question #6:* Is there a relationship between the pharmacokinetics of a Schedule II drug and indirect measures of driving ability?**

1. **A lack of evidence makes it impossible to draw evidence-based conclusions about the relationship between the pharmacokinetics of Schedule II drugs and driving ability (as measured by a simulator or on a prespecified driving course).**

   No studies of Schedule II drugs meeting the inclusion criteria of Key Question 6 addressed this outcome.

2. **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).**

   Three included studies demonstrated the existence of the relationship between the pharmacokinetics of Schedule II opioids (morphine, fentanyl, and meperidine) and temporal changes in measures of cognitive or psychomotor function.

3. **A lack of data makes it impossible to draw evidence-based conclusions about the relationship between the pharmacokinetics of a Schedule II opioid and temporal changes in measures of cognitive and psychomotor function in chronic licit users of the drugs.**

   No studies of Schedule II drugs meeting the inclusion criteria for Key Question 6 addressed this question in a population of chronic licit users of opioids.

4. **A paucity of evidence makes it impossible to draw evidence-based conclusions about the relationship between the pharmacokinetics of Schedule II stimulants and temporal changes in measures of cognitive or psychomotor function in healthy stimulant-naïve individuals.**

A single included study investigated the relationship between the pharmacokinetics of a Schedule II stimulant (dextroamphetamine) and temporal changes in cognitive or psychomotor function in healthy, stimulant-naïve individuals. This small, but otherwise high-quality study, demonstrated a temporal relationship between dextroamphetamine concentration and cognitive function. Because of the small size of the study, replication is required before evidence-based conclusions can be drawn.

5. **A lack of data makes it impossible to draw evidence-based conclusions about the relationship between the pharmacokinetics of Schedule II stimulants and temporal changes in measures of cognitive or psychomotor function in chronic licit users of the drugs.**

   No studies of Schedule II drugs meeting the inclusion criteria for Key Question 6 addressed this question in a population of chronic licit users of stimulants.

6. **A lack of evidence makes it impossible to draw evidence-based conclusions about the relationship between the pharmacokinetics of Schedule II depressants and temporal changes in measures of cognitive or psychomotor function.**

   No studies of Schedule II depressants met the inclusion criteria for Key Question 6.

7. **A lack of evidence makes it impossible to draw evidence-based conclusions about the relationship between the pharmacokinetics of Schedule II drugs and temporal changes in mood or behavior.**

   No studies of Schedule II drugs meeting the inclusion criteria for Key Question 6 addressed this outcome.

Key Question #7: Are there common drug interactions that include a prescribed Schedule II drug that increase the risk for a motor vehicle crash?

1. **No conclusions from direct evidence concerning the relationship between the serum level of a Schedule II drug and motor vehicle (any category) crash risk can be drawn at the present time.**

   Although our searches identified 14 potentially relevant articles, none was found to meet the retrieval criteria. Consequently, no evidence base currently exists that can be used to answer this question.

Key Question #8: Are there common drug interactions that include a prescribed Schedule II drug that affect indirect measures of driving ability?

1. **A paucity of data makes it impossible to draw evidence-based conclusions about the effect of combining a Schedule II drug with another drug on driving ability and cognitive or psychomotor function, mood or behavior.**

   Four relevant studies met the inclusion criteria for this report. Each study evaluated the effects of a different combination of one Schedule II drug with another drug. Because none of the studies was a high-quality mega-trial, replication is required before evidence-based conclusions about the effects of combining Schedule II drugs with other drugs can be drawn.

Conclusions

The fact that Schedule II controlled drugs are designed to interfere with neurochemical pathways in the brain leads to the expectation that these drugs may influence individuals' ability to perform complex tasks, such as driving. This expectation, combined with the wealth of incontrovertible evidence showing that individuals who abuse psychotropic drugs have a significantly increased risk for a motor vehicle crash, may lead to the hypothesis that individuals who take Schedule II controlled drugs for legitimate medical purposes will be at increased risk for a motor vehicle crash. The purpose of this evidence report is to determine whether currently available evidence supports that hypothesis.

On the Findings of this Evidence Report

The findings of the assessment, which are based on indirect measures of driving ability, suggest that use of Schedule II opioids or depressants may indeed pose a threat to road traffic safety when a driver first begins to use them. Evidence from several studies that administered the drugs to opioid- or depressant-naïve healthy individuals, though not providing strong evidence, has shown that simulated driving ability and high-level cognitive and psychomotor function are adversely affected by these drugs.

Studies of the effects of Schedule II stimulants do not provide evidence that the licit use of these drugs is likely to impair driver safety. However, evidence from several low-quality studies of chronic Schedule II opioid users who use the drugs for the treatment of chronic pain suggests that after a week or two of administration of the opioids at stable therapeutic doses, the adverse effects of the drugs diminish to the point that cognitive and psychomotor performance of licit long-term opioid users is indistinguishable from drivers who do not use the drugs. Whether the findings of these studies can legitimately be interpreted as providing evidence that long-term users of stable, therapeutic doses of a Schedule II opioid are at no greater risk for a crash than comparable individuals who are not using the drugs, is not clear at this time.

Because no studies of the long-term effects of licit Schedule II barbiturate use met the inclusion criteria for this evidence report, whether the observed short-term detrimental effects of such drugs on driving ability and cognitive or psychomotor function diminish with long-term use is unknown.

On the Limitations of this Evidence Report

The findings of this evidence report cannot be viewed as definitive. As with all systematic reviews, the soundness of the answers they provide is entirely dependent on the quality, quantity, consistency, robustness, and generalizability (to the specific target population of interest) of the available evidence. In this report, most of our evidence-based conclusions were supported by weak or moderate evidence. Also, because only two studies were generalizable to CMV drivers, the generalizability of the findings of this evidence report to this specific population is unclear.

Preface

Organization of Report

This evidence report contains five major sections: 1) *Background*, 2) *Current United States Federal Regulatory and Medical Advisory Criteria*, 3) *Methods*, 4) *Synthesis of Results*, and 5) a *Discussion section*. These major sections are supplemented by extensive use of appendices.

In the *Background* section, we provide background information about Schedule II drugs. In the *Methods* section, we detail how we identified and analyzed information for this report. The section covers the key questions addressed, details of literature searching, criteria for including studies in our analyses, evaluation of study quality, assessment of the strength of the evidence base for each question, and methods for abstracting and synthesizing clinical study results. The *Synthesis of Results* section of this report is organized by Key Question. For each question, we report on the quality and quantity of the studies that provided relevant evidence. We then summarize the available data extracted from included studies either qualitatively or, when the data permit, qualitatively and quantitatively (using meta-analysis). Each subsection in the *Synthesis of Results* section closes with our conclusions, which are based on our assessment of the available evidence. This evidence report ends with a *Discussion* section that briefly summarizes and discusses the findings of the report and puts them into context.

Scope

Of all occupations in the United States, workers in the trucking industry experience the third highest fatality rate, accounting for 12 percent of all worker deaths. About two-thirds of fatally injured truckers were involved in highway crashes. According to statistics from the United States Department of Transportation, 137,144 crashes involved a large truck in 2005. Of these, 59,405 were crashes that resulted in an injury to at least one individual for a total of 89,681 injuries. In 2004,[2] 4,862 large trucks were involved in fatal crashes for a total of 5,190 fatalities. This report aims to examine the relationship between licit Schedule II drug use and the risk for a motor vehicle crash. In order to meet the aims of this evidence report we address eight key questions. These eight key questions are as follows:

Key Question 1: Does the licit use of a prescribed Schedule II drug increase the risk for a motor vehicle crash?

Key Question 2: Does the licit use of a prescribed Schedule II drug negatively impact indirect measures of driving ability?

Key Question 3: What is the correlation between the serum level of a Schedule II drug and the risk for a motor vehicle crash?

Key Question 4: What is the correlation between the serum level of a Schedule II drug and indirect measures of driving ability?

[2] Fatality data for 2005 was not available at the time of writing.

Key Question 5: Is there a relationship between the pharmacokinetics of a Schedule II drug and the risk for a motor vehicle crash?

Key Question 6: Is there a relationship between the pharmacokinetics of a Schedule II drug and indirect measures of driving ability?

Key Question 7: Are there common drug interactions that include a prescribed Schedule II drug that increase the risk for a motor vehicle crash?

Key Question 8: Are there common drug interactions that include a prescribed Schedule II drug that affect indirect measures of driving ability?

Background

Of all occupations in the United States, workers in the trucking industry experience the third-highest fatality rate (http://www.bls.gov/iif/oshcfoiarchive.htm#2004charts), accounting for 12 percent of all worker deaths. About two-thirds of fatally injured truck workers were involved in highway crashes. According to statistics from the United States Department of Transportation (http://ai.volpe.dot.gov/CrashProfile/CrashProfileMainNew.asp?dy=2005), 137,144 non-fatal crashes involved a large truck in 2005. Of these, 59,405 were crashes that resulted in an injury to at least one individual for a total of 89,681 injuries. In 2004,[3] 4,862 large trucks were involved in fatal crashes for a total of 5,190 fatalities (http://ai.volpe.dot.gov/CrashProfile/CrashProfileMainNew.asp?dy=2004). The purpose of this evidence report is to assess and summarize the available data pertaining to the relationship between the licit use of Schedule II drugs and CMV safety.

Schedule II Drugs

The Controlled Substances Act (CSA) was enacted into law by the Congress of the United States as Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970. This statute is the legal basis by which the manufacture, importation, possession, and distribution of certain drugs are regulated by the federal government of the United States. The Act also served as national implementing legislation for the Single Convention on Narcotic Drugs.

The CSA created five Schedules (classifications), with varying qualifications that determine whether a drug should be included in the controlled substances listing. Two federal departments, the Department of Justice (DOJ) and the Department of Health and Human Services (HHS, which includes the Food and Drug Administration [FDA]) determine which specific drugs are added or removed from the various Schedules; though the statute passed by Congress created the initial listing of controlled substances. Classification decisions are required to be made on the criteria of potential for abuse, accepted medical use in the United States, and potential for addiction (Table 2).

[3] Fatality data for 2005 was not available at the time of writing.

Table 2. Controlled Substances Act Schedules

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

Schedule II drugs are controlled drugs that have a legitimate medical purpose but, at the same time, carry a high potential for the development of physical and psychological dependence. The types of drugs that fall into the category of a Schedule II controlled drug include various stimulants (amphetamines and methylphenidate), depressants (several barbiturates and glutethimide), and a large number of opioids. A complete list of Schedule II drugs can be found at the U.S. DEA Web site: http://www.dea.gov/pubs/scheduling.html.

Stimulants–Amphetamines and Methylphenidate

Stimulants are used to treat narcolepsy and most commonly, ADHD. Stimulants have also been used as weight control drugs. Schedule II stimulants that are commonly prescribed in the United States include amphetamine, dextroamphetamine (Dexedrine®, DextroStat®), methamphetamine (Desoxyn®), and methylphenidate (Ritalin®). Cocaine is also a Schedule II stimulant, but its only use in modern medicine is as an anesthetic. Consequently, it is highly unlikely that anyone using cocaine outside of a medical setting is doing so legally.

Depressants–Barbiturates and Glutethimide

Depressants that fall within Schedule II include some barbiturates and glutethimide. Today, there is little medical use of glutethimide in the United States so the focus of our discussions of depressants in this evidence report primarily concentrates on barbiturates. Barbiturates produce a wide spectrum of central nervous system depression ranging from mild sedation to coma. They have been used medically as sedatives, hypnotics, anesthetics, and anticonvulsants. Until the benzodiazepines were introduced in the 1960s, barbiturates were widely used clinically for a range of indications, including the treatment of anxiety, insomnia, seizure disorders, and as muscle relaxants and anesthetic agents. Benzodiazepines and the newer non-benzodiazepine hypnotics are now preferred

over barbiturates for most of these clinical uses because they have a wider therapeutic index, tolerance develops more slowly, and their liability for abuse is lower than that of the barbiturates.

Schedule II barbiturates include amobarbital (Amyta®), pentobarbital (Nembutal®), secobarbital (Seconal®), and Tuinal (an amobarbital/secobarbital combination product). These drugs are primarily used outside of the hospital setting (where they are used for preoperative sedation) for the treatment of insomnia.

Opioids–Opioids and Synthetic Narcotic Analgesics

Opioid is a general term that includes the opiates and synthetic narcotic analgesics. Opiates are narcotic analgesics derived from the opium poppy. Morphine and codeine (both Schedule II drugs) are extracted from the Asian poppy *Papaver somniferum*. Commonly used Schedule II opiates that are derived from morphine include hydromorphone, oxycodone, and hydrocodone. Commonly used synthetic opioids include pethidine or meperidine (Demerol®), methadone, pentazocine (Talwin®), propoxyphene (Darvon®), butorphanol (Stadol NS®), and diphenoxylate (Lomotil®).

The most common reason for the licit use of opioids in individuals who are likely to drive a commercial motor vehicle is for the treatment of chronic pain. Opioids do, however, have other legitimate medical uses other than to treat pain. For example, codeine and hydrocodone are common ingredients found within cough syrups (for example, Tussionex® and Novahistex DH®).

Some opioid analgesics are used to treat drug addiction and dependence. Methadone has been used for many years to treat opioid addicts. The treated individual becomes addicted to the methadone but has a stable supply of legal opioid and is then often able to participate in other aspects of treatment, live a more normal life, and find employment. Methadone has a number of advantages over other opioids. It can be taken orally; it is long-acting; and it can be taken only once a day. Because of cross-tolerance, methadone blocks the effects of usual doses of other opioids so the user does not get “high” and has no incentive to continue using them. Methadone maintenance programs, which continue supplying the drug, may be followed by methadone withdrawal, in which the person is slowly weaned from the drug. An evaluation of methadone drug addiction treatment programs and commercial vehicle driver safety is beyond the scope of the present evidence report.

Prevalence and Incidence of Licit Schedule II Drug Use

The potential for misuse of Schedule II controlled substances has resulted in a high level of interest in controlled drug abuse and an apparently corresponding lack of interest in data pertaining to the licit use of these substances. Consequently, our searches identified a plethora of information related to estimates of the incidence and prevalence of illicit drug use but we found no publicly available data on estimates of the prevalence and incidence of licit controlled drug use. Having said this, some information about licit Schedule II drug use is available.

According to statistics from the National Health and Nutrition Examination Survey (NHANES III), prescription analgesic use (including opioids) in the United States was

9%, with females more likely than males to use prescription analgesics (11% of females versus 7% of males,
p <0.001).(1) Using data obtained from the U.S. Drug Abuse Warning Network and Automation of Reports (DAWN) and Consolidated Orders Systems (ARCOS) for the years 1990 through 1996, Joranson et al.(2) estimated that there were increases in medical use of morphine of 59%, fentanyl of 1168%, oxycodone of 23% and hydromorphone of 19%. At the same time a decrease in the medical use of meperidine of 35% was observed. In an update to this report, which included data from the DAWN and ARCOS databases for 1997–2002, Gilson et al.(3) found the further increases in the medical use of morphine (73.30%), fentanyl (226%), oxycodone (402.9%) and hydromorphone (96.35%) and further reductions in the medical use of meperidine (6.13%).

According to statistics provided by the U.S. DEA(4), there has been a 2,000% increase in the legal manufacture of stimulants between 1990 and 2000, with most of this increase being attributed to the ADHD medication methylphenidate (Ritalin®). While initially prescribed for children and adolescents, methylphenidate has now become more widely prescribed among adult populations for ADHD and attention deficit disorder (ADD).

Federal Regulatory and Medical Advisory Criteria for CMV Operators Pertaining to Controlled Substances

Current Federal Regulatory Criteria for CMV Operators

FMCSA regulations, found in 49 Code of Federal Regulations (CFR) 301 through 399, cover businesses that operate CMVs in interstate commerce. FMCSA regulations that pertain to fitness to drive a CMV are found in 49 CFR 391 Subpart E. Only motor carriers engaged purely in intrastate commerce are not directly subject to these regulations. However, intrastate motor carriers are subject to State regulations, which must be identical to, or compatible with, the Federal regulations in order for States to receive motor carrier safety grants from the FMCSA. States have the option of exempting CMVs with a gross vehicle weight rating of less than 26,001 lb.

The following subsection contains the federal regulatory and medical advisory standards found in the Federal Motor Carrier Safety Regulations (49 C.F.R. section 391.41) which specifically apply to drivers who use prescription drugs. Complete Federal Motor Carrier Safety Regulations can be found at the following web site:
http://www.fmcsa.dot.gov/rules-regulations/administration/fmcsr/fmcsrguide.asp?section_type=A.

§382.105: Guidance for Regulations on Controlled Substance Use and Testing

Guidance: Possession or use of controlled substances are prohibited when operating a CMV under the FHWA regulations regardless of the source of the substance. A limited exception exists for a substance's use in accordance with instructions provided by a licensed medical practitioner who knows that the individual is a CMV driver who operates in a safety-sensitive job and has provided instructions to the CMV driver that the use of the substance will not affect his or her ability to safely operate a CMV (see §382.213, 391.41(b)(12), and 392.4(c)). Individuals entering the United States must

properly declare controlled substances with the U.S. Customs Service (see 21 CFR 1311.27).

The FHWA expects medical review officers (MROs) to properly investigate the facts concerning a CMV driver's claim that a positive controlled substance test result was caused by a prescription written by a knowledgeable, licensed medical practitioner or the use of an over-the-counter substance that was obtained in a foreign country without a prescription. This investigation should be documented in the MRO's files.

If the CMV driver lawfully obtained a substance in a foreign country without a prescription which is a controlled substance in the United States, the MRO must also investigate whether a knowledgeable, licensed medical practitioner provided instructions to the driver that the use of the over-the-counter substance would not affect the driver's ability to safely operate a CMV.

Potential violations of §392.4 must be investigated by the law enforcement officer at the time possession or use is discovered to determine whether the exception applies.

Subpart E: Physical Qualifications and Examinations

§391.41 Physical qualifications for drivers

(a) A person shall not drive a commercial motor vehicle unless he/she is physically qualified to do so and, except as provided in §391.67 (Farm vehicle drivers of articulated CMVs), has on his/her person the original, or a photographic copy, of a medical examiner's certificate that he/she is physically qualified to drive a commercial motor vehicle.

(b)(12)(i) Does not use a controlled substance identified in 21 CFR 1308.11 Schedule I, an amphetamine, a narcotic, or any other habit-forming drug.

(b)(12)(ii) *Exception*. A driver may use such a substance or drug, if the substance or drug is prescribed by a licensed medical practitioner who:

(b)(12)(ii)(A) Is familiar with the driver's medical history and assigned duties; and

(b)(12)(ii)(B) Has advised the driver that the prescribed substance or drug will not adversely affect the driver's ability to safely operate a commercial motor vehicle.

§391.41(b)(12) Medical Advisory Criteria

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

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

Exception: A driver may use such a substance or drug if the substance or drug is prescribed by a licensed medical practitioner who is familiar with the driver's medical history and assigned duties, and has advised the driver that the prescribed substance or drug will not adversely affect the driver's ability to safely operate a CMV. This exception does not apply to the use of methadone.

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

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

The term "uses" is designed to encompass instances of prohibited drug use determined by a physician through established medical means. This may or may not involve body fluid testing. If body fluid testing takes place, positive test results should be confirmed by a second test of greater specificity. The term "habit forming" is intended to include any drug or medication generally recognized as capable of becoming habitual, and which may impair the user's ability to operate a CMV safely.

The driver is medically unqualified for the duration of the prohibited drug(s) use and until a second examination shows the driver is free from the prohibited drug(s) use. Recertification may involve a substance abuse evaluation, the successful completion of a drug rehabilitation program, and a negative drug test result. Additionally, given that the certification period is normally 2 years, the examiner has the option to certify for a period of less than 2 years if this examiner determines more frequent monitoring is required.

See Conference on Neurological Disorders and Commercial Drivers and Conference on Psychiatric Disorders and Commercial Drivers at:
http://www.fmcsa.dot.gov/rulesregs/medreports.htm.

Subpart B: Prohibitions

§382.213 Controlled substances use

(a) No driver shall report for duty or remain on duty requiring the performance of safety-sensitive functions when the driver uses any controlled substance, except when the use is pursuant to the instructions of a licensed medical practitioner, as defined in §382.107, who has advised the driver that the substance will not adversely affect the driver's ability to safely operate a commercial motor vehicle.

(b) No employer having actual knowledge that a driver has used a controlled substance shall permit the driver to perform or continue to perform a safety-sensitive function.

(c) An employer may require a driver to inform the employer of any therapeutic drug use.

[66 FR 43106 August 17, 2001]

§392.4 Drugs and other substances

(a) No driver shall be on duty and possess, be under the influence of, or use, any of the following drugs or other substances:

(a)(1) Any 21 CFR 1308.11 Schedule I substance;

(a)(2) An amphetamine or any formulation thereof (including, but not limited, to "pep pills," and "bennies");

(a)(3) A narcotic drug or any derivative thereof; or

(a)(4) Any other substance, to a degree which renders the driver incapable of safely operating a motor vehicle.

(b) No motor carrier shall require or permit a driver to violate paragraph (a) of this section.

(c) Paragraphs (a)(2), (3), and (4) do not apply to the possession or use of a substance administered to a driver by or under the instructions of a licensed medical practitioner, as defined in §382.107 of this subchapter, who has advised the driver that the substance will not affect the driver's ability to safely operate a motor vehicle.

(d) As used in this section, "possession" does not include possession of a substance which is manifested and transported as part of a shipment.

(49 U.S.C. 3102; 49 CFR 1.48 and 301.60)

[49 FR 44215, Nov. 5, 1984, as amended at 53 FR 18057, May 19, 1988; 60 FR 38746, July 28, 1995].

Brief History of CMV Driver and Drug Policy

Beginning December 23, 1993, the Federal Highway Administration (FHWA) required CMV carriers subject to 49 CFR part 391 to utilize controlled substance testing and to collate this data into annual reports (58 FR 68220). On February 15, 1994 this requirement was amended to include the similar alcohol rule report (59 FR 7484), and on March 13, 1995, the data collection rules were revised by the FHWA to reduce the burden of data gathering on CMV carriers (60 FR 13369). In addition, CMV carriers were required to use 49 CFR part 382, which superseded 49 CFR part 391. The final rule for the controlled substance and alcohol implementation and testing policy was published in the March 8, 1996 Federal Register (61 FR 9546), and contained amendments to 49 CFR parts 382, 383, 390, 391, and 392, including corrections to errors in the February 15, 1994 final rule.

On October 3, 2005, the FMCSA announced that the department was undertaking the scientific review of medical research topics pertinent to the CMV industry in order to prioritize its medical standards review and development work. Among the topics chosen for review were: Controlled Substances; Diabetes Mellitus; Cardiovascular; Vision; Neurology; and Hearing.

Current Drug Testing Policy

Current Department of Transportation drug testing (49 CFR Part 40) rules require drivers who operate CMVs that require a commercial driver's license to undergo drug tests under

the following schedule: pre-employment; reasonable suspicion; post-crash; random; return-to-duty; and on follow-up.[4]

Drug testing is conducted by analyzing a driver's urine specimen. All urine specimens are analyzed for the following drugs:

1. Marijuana (THC metabolite):
2. Cocaine
3. Amphetamines
4. Opiates (including heroin)
5. Phencyclidine (PCP)

The analysis is performed at laboratories certified and monitored by the HHS. The driver provides a urine specimen which is sealed and labeled by a "collector." The collector completes a chain of custody document and prepares the specimen and accompanying paperwork for shipment to an HHS-certified drug-testing laboratory. Specimen collection procedures are designed to ensure that the specimen's security, proper identification and integrity are not compromised. The Omnibus Transportation Employee Testing Act of 1991 requires that drug testing procedures for CMV drivers include split specimen procedures. That is, each urine specimen is subdivided into two specimen bottles labeled as a "primary" and "split." Only the primary specimen is opened and used for the urinalysis. The split specimen bottle remains sealed and is stored at the laboratory. If the analysis of the primary specimen confirms the presence of illegal, controlled substances, the driver has 72 hours to request the split specimen be sent to another HHS-certified laboratory for analysis.

The drug testing procedure is a two-stage process. First, a screening test is performed. If it is positive for one or more of the drugs listed above, a confirmatory gas chromatography/mass spectrometry (GC/MS) analysis is performed. The purpose of GC/MS confirmation is to ensure that over-the-counter medications or preparations are not falsely reported as positive results.

All drug test results are carefully reviewed and interpreted by an MRO. If the laboratory reports a positive result to the MRO, the MRO contacts the driver (in person or by telephone) and conducts an interview to determine if there is an alternative medical explanation for the presence of the drugs found in the driver's urine specimen. If the driver provides appropriate documentation and the MRO determines that it is legitimate medical use of the prohibited drug, the drug test result will be reported as negative to the driver's employer.

Subpart B: Prohibitions

§382.215 Controlled Substances Testing

No driver shall report for duty, remain on duty or perform a safety-sensitive function, if the driver tests positive or has adulterated or substituted a test specimen for controlled substances. No employer having actual knowledge that a driver has tested positive or has

[4] Complete details of the FMCSA Alcohol and Drug Testing Rules can be found at the following web site: http://www.dot.gov/ost/dapc/NEW_DOCS/part40.html?proc.

adulterated or substituted a test specimen for controlled substances shall permit the driver to perform or continue to perform safety-sensitive functions.

Methods

The *Methods* section provides a synopsis of how we identified and analyzed information for the report. The section briefly covers the key questions addressed, literature searches performed, the criteria used including studies, evaluation of study quality, assessment of the strength of the evidence base for each key question, and the methods used for abstracting and analyzing available data. Specific details of literature searches, study quality assessment, statistical approaches used, etc. are documented in appendices.

Key Questions

This evidence report addresses eight key questions. These key questions, which were developed by the FMCSA in collaboration with ECRI, are listed below:

Key Question 1: Does the licit use of a prescribed Schedule II drug increase the risk for a motor vehicle crash?

Key Question 2: Does the licit use of a prescribed Schedule II drug negatively impact indirect measures of driving ability? Indirect measures of driving ability include the following:

a) Measures of driving-related performance (laboratory and experimental)

b) Measures of cognitive or psychomotor function

c) Measures of behavior (risk taking behavior, aggression, etc.)

Key Question 3: What is the correlation between the serum level of a Schedule II drug and the risk for a motor vehicle crash?

Key Question 4: What is the correlation between the serum level of a Schedule II drug and indirect measures of driving ability? Indirect measures of driving ability include the following:

a) Measures of driving-related performance (laboratory and experimental)

b) Measures of cognitive or psychomotor function

c) Measures of behavior (risk taking behavior, aggression, etc.)

Key Question 5: Is there a relationship between the pharmacokinetics of a Schedule II drug and the risk for a motor vehicle crash?

Key Question 6: Is there a relationship between the pharmacokinetics of a Schedule II drug and indirect measures of driving ability? Indirect measures of driving ability include the following:

a) Measures of driving-related performance (laboratory and experimental)

b) Measures of cognitive or psychomotor function.

c) Measures of behavior (risk taking behavior, aggression, etc.)

Key Question 7: Are there common drug interactions that include a prescribed Schedule II drug that increase the risk for a motor vehicle crash?

Key Question 8: Are there common drug interactions that include a prescribed Schedule II drug that affect indirect measures of driving ability? Indirect measures of driving ability include:

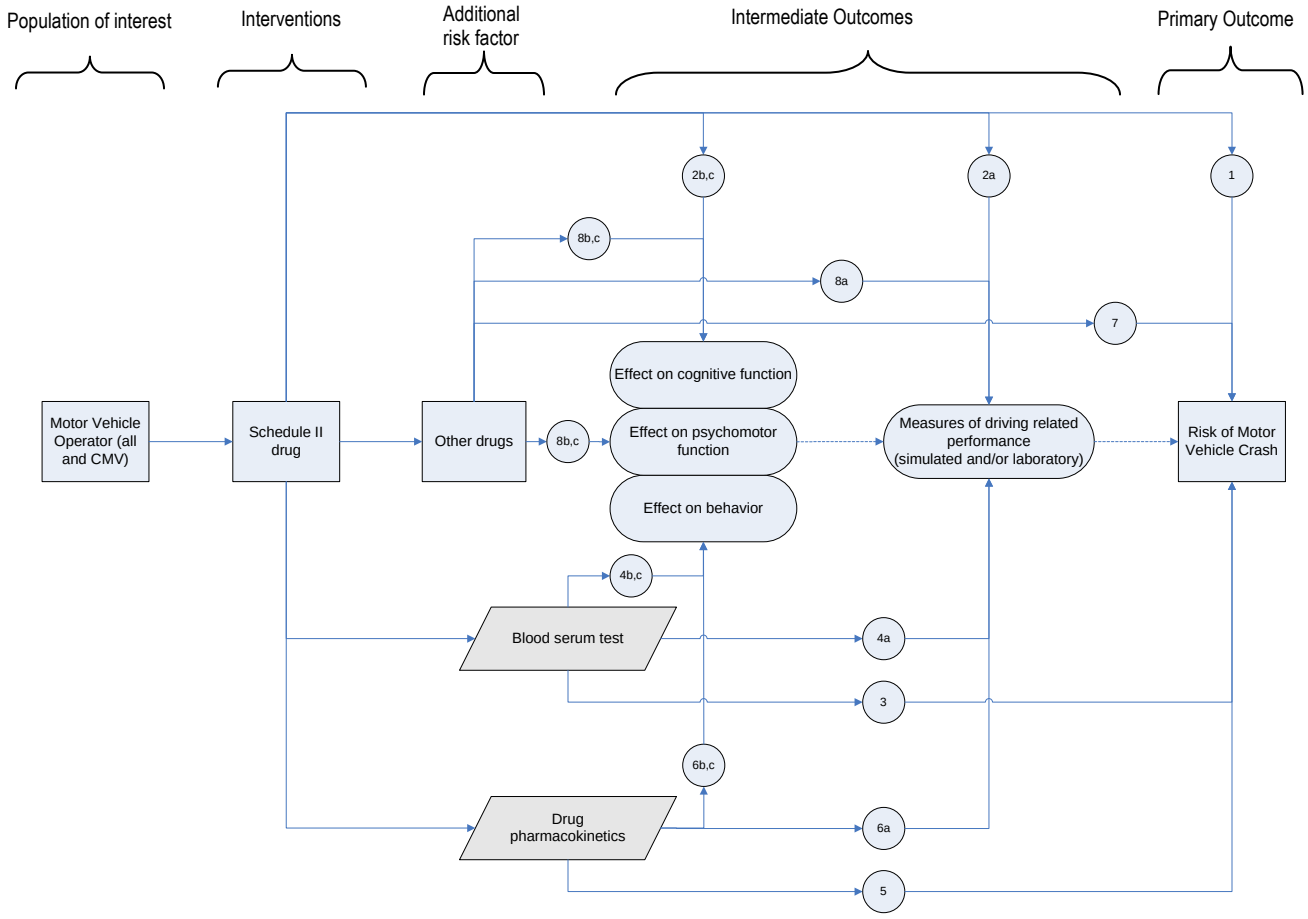
a) Measures of driving-related performance (laboratory and experimental)

b) Measures of cognitive or psychomotor function

c) Measures of behavior (risk taking behavior, aggression, etc.)

The eight key questions listed above are put into context by the logic framework presented in Figure 1. The logic framework shows the logical relationships between the population(s) of interest, the risk factor(s) of interest, intervention(s) of interest, intermediate outcome(s), and the outcome of primary importance; in this case, crash risk.

Figure 1. Logic Framework



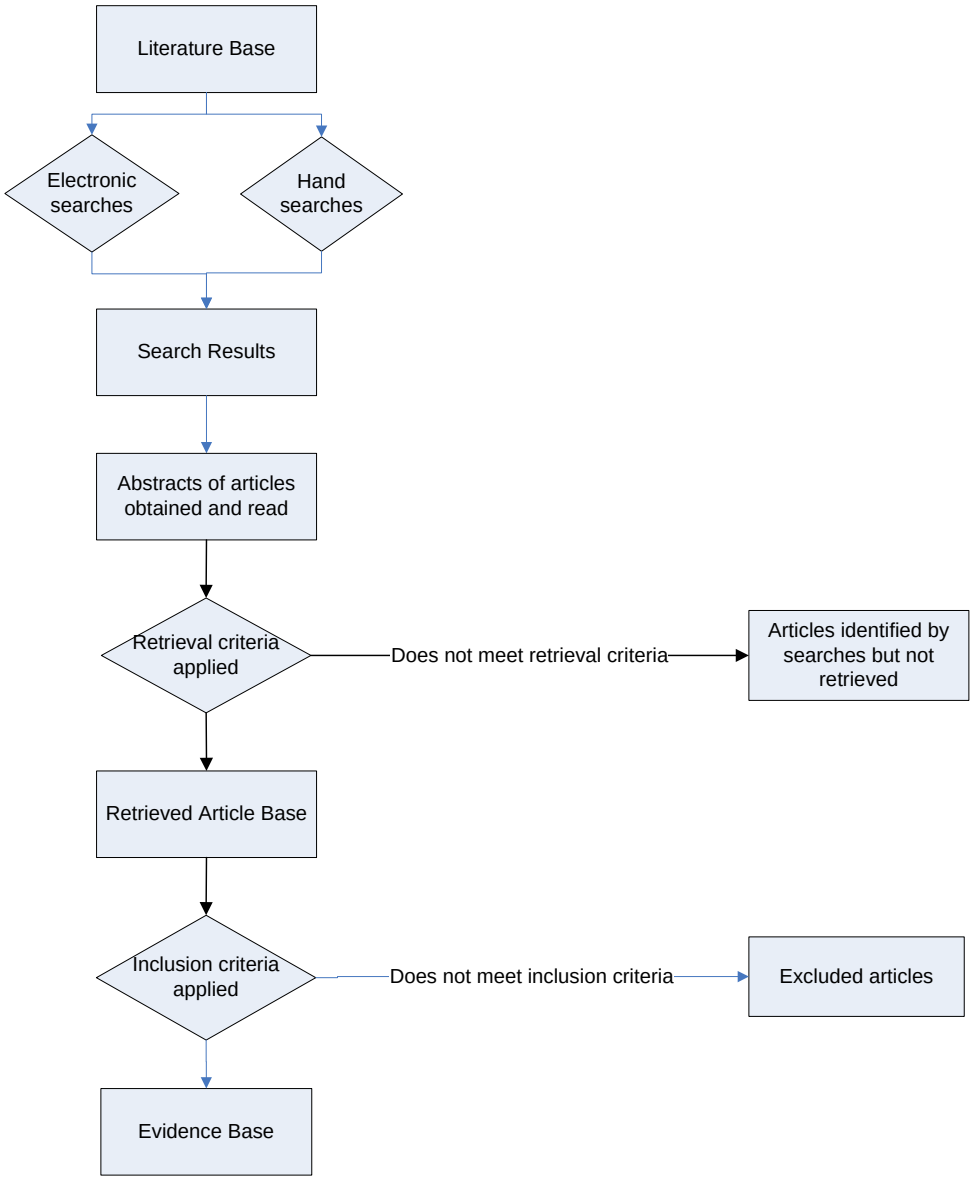
The numbered lines in the framework map onto the key questions that we will address in the present evidence report. Dashed lines indicate relationships that are not addressed by a key question. For example, the dashed line in the logic framework indicates that there is

a relationship between driving ability as evaluated in a driving simulator and the risk for a motor vehicle crash. This dashed line acknowledges the existence of a link but makes it clear that we will not be evaluating this relationship in the present evidence report. We note that the strength of the relationship between intermediate outcomes and the primary outcome can be influenced by a number of modifiable determinants. Modifiable determinants are variables that affect the pathway and each other and include the following: other personal risk factors (e.g., hours of sleep the previous night), vehicle risk factors (e.g., brake adjustment), environmental factors (e.g., weather and roadway features), and risks created by other drivers and traffic.

Identification of Evidence Bases

The individual evidence bases for each of the eight key questions addressed in this evidence report were identified using the multistage process that is captured by the algorithm presented in Figure 2. The first stage of this process consists of a comprehensive search of the literature. Searches for this evidence report were conducted by ECRI's team of information specialists. The second stage of the process consists of the examination of abstracts of identified studies in order to determine which articles will be retrieved. The final stage of the process consists of the selection of the actual articles that will be included in the evidence base.

Figure 2. Evidence Base Identification Algorithm



Searches

One characteristic of a good evidence report is a systematic and comprehensive search for information. Such searches distinguish systematic reviews from traditional literature reviews which tend to use a less rigorous approach to identifying and obtaining literature thereby allowing a reviewer to include only articles that agree with a particular perspective and to ignore articles that do not. Our approach precludes this potential reviewer bias because we obtain and include articles according to explicitly determined *a priori* criteria. Full details of the search strategies used in this report are presented in Appendix A.

Electronic Searches

We performed comprehensive searches of the electronic databases listed in Table 3.

Table 3. Electronic Databases Searched

Name of database	Date limits	Platform/provider
Cochrane Library	Through 2006, Issue 2	www.thecochranelibrary.com
Embase (Excerpta Medica)	1980 through May 31, 2006	OVID
Medline	1966 through May 31, 2006	OVID
PubMed (Pre Medline)	Premedline[sb] Searched May 31, 2006	www.pubmed.gov
PsycINFO	1968 through May 31, 2006	http://www.apa.org/psycinfo/
TRIS Online (Transportation Research Information Service Database)	Through May 31, 2006	http://trisonline.bts.gov/search.cfm

Manual Searches

We reviewed journals and supplements maintained in ECRI's collections of more than 1,000 periodicals. Non-journal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. In addition, we examined the reference lists of all obtained articles with the aim of identifying relevant reports not identified by our electronic searches. In order to retrieve additional relevant information, we also performed hand searches of the "gray literature." Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. These latter documents do not appear in the peer-reviewed journal literature.

Retrieval Criteria

Retrieval criteria were used to determine whether a full-length version of an article identified by our searches should be ordered. Decisions pertaining to whether a full-length article should be retrieved are usually based on a review of available abstracts. For this project, retrieval criteria were determined *a priori* in conjunction with the FMCSA. These retrieval criteria are presented in Appendix B.

If an article did not meet the retrieval criteria for this evidence report, the full-length version of the article was not obtained. If it was unclear whether a potentially relevant article met our retrieval criteria (e.g., no abstract was available for evaluation), the full-length version of that article was obtained.

Inclusion and Exclusion Criteria

Each retrieved article was read in full by an ECRI analyst who determined whether that article met a set of predetermined, question specific, inclusion criteria. As was the case for the retrieval criteria, the inclusion criteria for this evidence report were determined *a*

priori in conjunction with the FMCSA. These inclusion and exclusion criteria are presented in Appendix C.

If on reading an article, it was found not to meet the question specific inclusion criteria listed in Appendix C, the article was excluded from the analysis. Each excluded article, along with the primary reason for its exclusion, are presented in Appendix D.

Evaluation of Quality of Evidence

Rather than focus on the quality of the individual studies that comprise an evidence base, our approach to assessing the quality of evidence focused on the overall *body* of the available evidence used to draw an evidence-based conclusion. Using this approach, which is described in Appendix E, we take into account not only the quality of the individual studies that comprise the evidence base for each key question, we also consider the interplay between the quality, quantity, robustness, and consistency of the overall body of evidence.

Our approach to assessing the strength of the body of evidence makes a clear distinction between a qualitative conclusion (e.g., "Individuals taking a licit Schedule II drug for chronic non-malignant pain are at increased risk for a motor vehicle crash") and a quantitative conclusion (e.g., When compared to individuals not using a legally prescribed Schedule II drug for chronic pain, the relative risk for a motor vehicle crash among individuals taking such a drug is 1.37; 95% CI: 1.03–2.03; P <0.005).

As shown in Table 4, we assigned a separate strength of evidence rating to each of type of conclusion. Evidence underpinning a qualitative conclusion was rated according to its strength, and evidence underpinning quantitative conclusions was rated according to the stability of the effect size estimate that was calculated.

Table 4. Strength of Evidence Ratings for Qualitative and Quantitative Conclusions

Strength of Evidence	Interpretation
Qualitative Conclusion	
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. ECRI recommends regular monitoring of the relevant literature for moderate-strength conclusions.
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. ECRI recommends frequent monitoring of the relevant literature.
Unacceptably Weak	Although some evidence exists, the evidence is insufficient to warrant drawing an evidence-based conclusion. ECRI recommends frequent monitoring of the relevant literature.
Quantitative Conclusion (Stability of Effect Size Estimate)	
High	The estimate of treatment effect in the conclusion is stable. It is highly unlikely that the magnitude of this estimate will change substantially as a result of the publication of new evidence.
Moderate	The estimate of treatment effect in the conclusion is somewhat stable. There is a small chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI recommends regular monitoring of the relevant literature.
Low	The estimate of treatment effect included in the conclusion is likely to be unstable. There is a reasonable chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI recommends frequent monitoring of the relevant literature.

Strength of Evidence	Interpretation
Unstable	Estimates of the treatment effect are too unstable to allow a quantitative conclusion to be drawn at this time. ECRI recommends frequent monitoring of the relevant literature.

The definitions presented in the table above are intuitive. Qualitative conclusions that are supported by strong evidence are less likely to be overturned by the publication of new data than conclusions supported by weak evidence. Likewise, quantitative effect size estimates that are deemed to be stable are more unlikely to change significantly with the publication of new data than are unstable effect size estimates.

Statistical Methods

Our intent in performing a systematic review is always to perform a meta-analysis. This evidence report was no exception. However, in this case the data extracted from the studies that formed the evidence bases for this evidence report were not compatible with pooling using meta-analysis. Consequently, our assessment of the evidence included in this evidence report is limited to a qualitative assessment.

Synthesis of Results

This section summarizes the findings of our assessment for each of the eight key questions that we addressed in this evidence report.

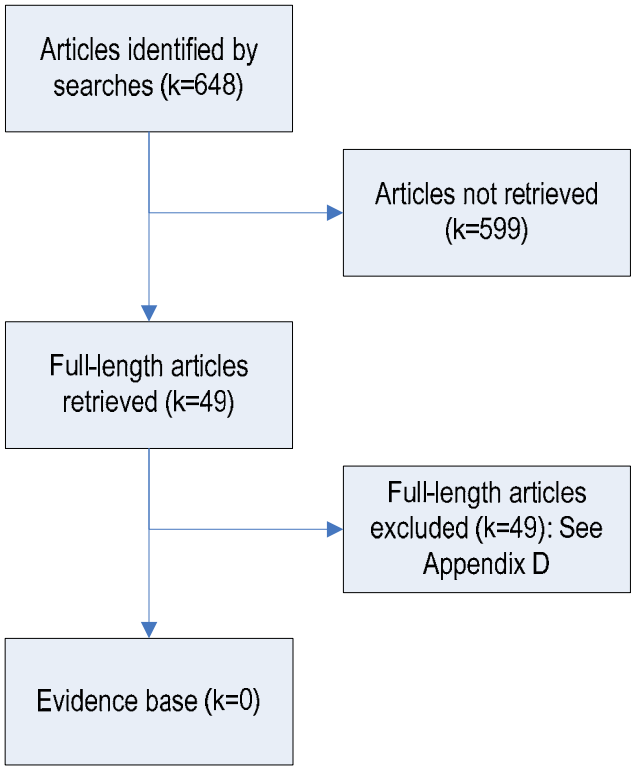
Key Question 1: Does the licit use of a prescribed Schedule II drug increase the risk for a motor vehicle crash?

In attempting to answer this question we searched for comparative trials that compared motor vehicle crash risk among individuals treated for a condition that required the use of a Schedule II drug and individuals not treated with such drugs who were otherwise comparable.

Identification of Evidence Base

The identification of the evidence base for Key Question 1 is summarized in Figure 3. Our searches[5] identified a total of 648 articles that appeared relevant to this key question. On comparing the abstracts for these articles against the retrieval criteria for this question listed in Appendix B, 49 full-length articles were retrieved. On reading each of the 49 articles in full we found that none met the inclusion criteria for this key question. Table D-1 of Appendix D lists the 49 articles that were retrieved but then excluded.

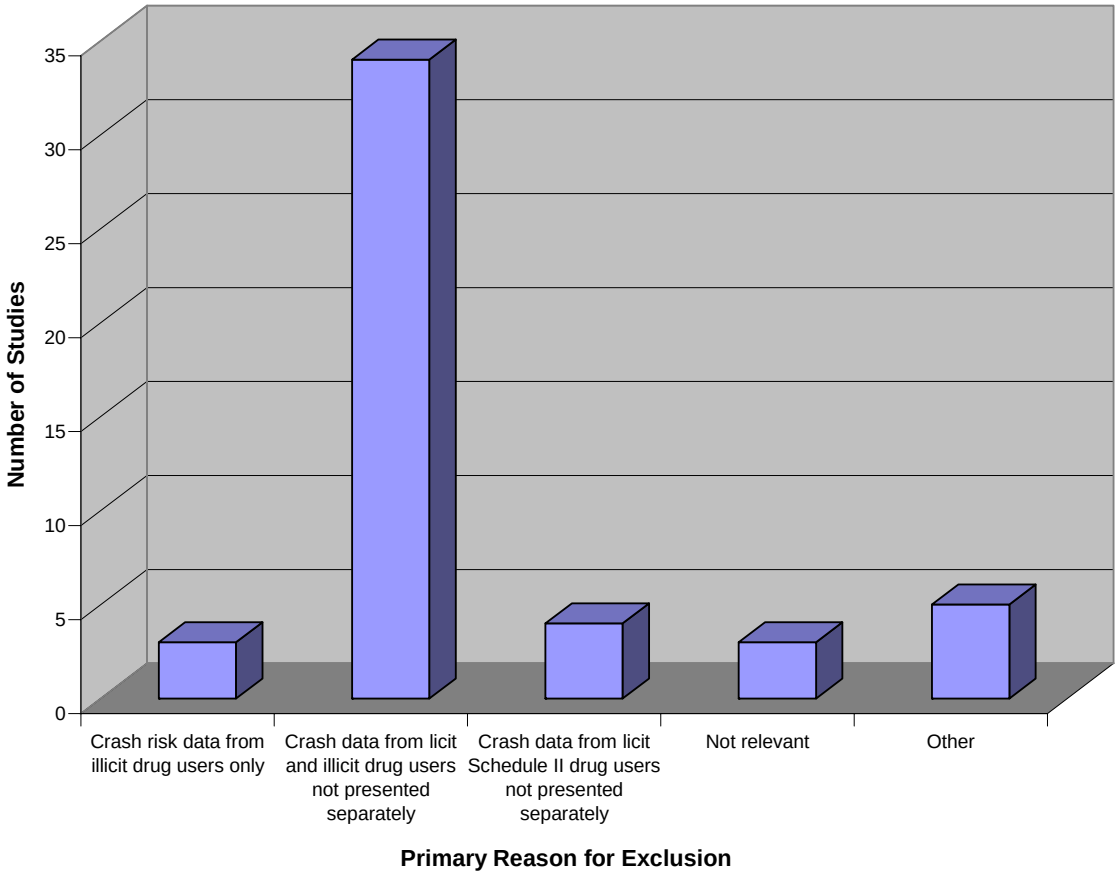
Figure 3. Development of Evidence Base for Key Question 1



[5] See Appendix A for search strategies.

The primary reasons for the exclusion of the 49 retrieved articles are presented in Figure 4. The primary reason for article exclusion was the combination of crash data from licit and illicit users in most (34 studies) of the identified studies. Because illicit drug users do not use drugs in a manner that is compatible with a therapeutic regimen (the aim of a drug abuser is to use the drug to deliberately initiate a change in mental state whereas, the aim of a licit user is to treat a disorder), crash data that includes drug abusers cannot provide an answer to Key Question 1. The second most common reason for exclusion was that several studies which were designed to examine the crash risk associated with a particular drug class encompassed drugs that spanned several drug schedules (four studies). Not all opioids, stimulants, and depressants are Schedule II drugs and studies that evaluated crash risk by drug class did not stratify crash risk data by United States DEA drug schedule.

Figure 4. Frequency of "Reasons for Study Exclusion"



Section Summary

No conclusions from direct evidence concerning the relationship between the licit use of a Schedule II drug and motor vehicle (of any category) crash risk can be drawn at the present time.

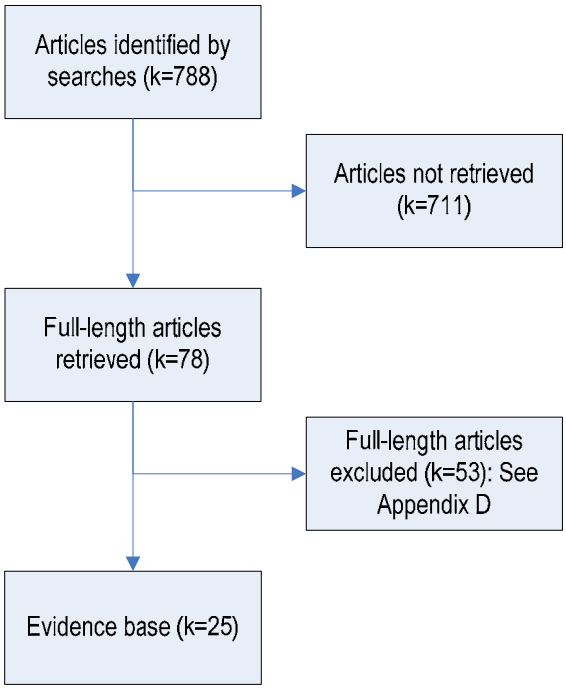
Although we identified and retrieved 49 articles that described 49 unique studies none met the inclusion criteria for this key question.

Key Question 2: Does the licit use of a prescribed Schedule II drug negatively impact indirect measures of driving ability?

Identification of Evidence Base

The identification pathway of the evidence base for Key Question 2 is summarized in Figure 5. Our searches[6] identified a total of 788 articles that appeared relevant to this key question. Following application of the retrieval criteria[7] for this question, 78 full-length articles were retrieved and read in full. Fifty-three of the retrieved articles were found not to meet the inclusion criteria[8] for this key question. Table D-2 of Appendix D lists the 53 articles that were retrieved but later excluded because they did not meet the inclusion criteria for Key Question 2. The table also provides the primary reason that each article was excluded.

Figure 5. Development of Evidence Base for Key Question 2



[6] See Appendix A for search strategies
[7] See Appendix B for retrieval criteria
[8] See Appendix C for inclusion criteria

Table 5 lists the 25 articles meeting the inclusion criteria for Key Question 2. Complete descriptions of the studies included in the evidence base for this key question are presented in *Study Summary Tables* that comprise Appendix G.

Table 5. Evidence Base for Key Question 2

Reference	Year	Study Location	Country
Barkley et al.(5)	2005	South Carolina	USA
Byas-Smith et al.(6)	2005	Georgia	USA
Sliber et al.(7)	2005	Hawthorn	Australia
Sabatowski et al.(8)	2003	Cologne	Germany
Mills et al.(9)	2001	North Carolina	USA
Sjogren et al.(10)	2000	Copenhagen	Denmark
Moulin et al.(11)	1996	Ontario	Canada
Vaino et al.(12)	1995	Helsinki	Finland
Coda et all.(13)	1994	Washington	USA
Kerr et al.(14)	1991	Washington	USA
Clark et al.(15)	1986	South Australia	Australia
Clark et al.(16)	1986	South Australia	Australia
Saarialho-Kere et al.(17)	1986	Helsinki	Finland
Logsdon et al.(18)	1984	Oklahoma	USA
Redpath et al.(19)	1982	Manchester	England
Pishkin et al.(20)	1980	Oklahoma	USA
Hindmarch et al.(21)	1979	London	England
Tansella et al.(22)	1979	Verona and London	Italy and England
Ghoneim et al.(23)	1975	Iowa	USA
Kortilla et al.(24)	1975	Helsinki	Finland
Kopriva et al.(25)	1974	Srobarova	Czechoslovakia
Linnoila et al.(26)	1973	Helsinki	Finland
Betts et al.(27)	1972	Alabama	USA
Jeffrey et al.(28)	1972	Louisiana	USA
Malpas et al.(29)	1970	London	England

Evidence Base

This subsection provides a brief description of the key attributes of the 25 studies that comprise the evidence base for Key Question 2. Here we discuss relevant information as it pertains to the quality of the included studies and their generalizability to drivers of CMVs.

As mentioned earlier, Schedule II drugs primarily consist of three general drug classes; stimulants, depressants, and opioids. Without exception, the included studies evaluated the effects of a single drug from one of these drug categories (Table 6). Because

stimulants, depressants, and opioids have distinctly different mechanisms of action, and because these drug classes are used to treat distinctly different medical conditions, we consider the available evidence for each drug class separately. Thus, the evidence base used to evaluate the effects of stimulants on the outcomes measures of interest in this section of the evidence report consists of six studies, the evidence base for the effects of depressants consists of seven studies, and the evidence base for the effects of opioids consists of 12 studies.

Table 6. Drug Classes Assessed by Included Study

Reference	Year	Depressant	Opioid	Stimulant
Barkley et al.(5)	2005			✓
Byas-Smith et al.(6)	2005		✓	
Sliber et al.(7)	2005			✓
Sabatowski et al.(8)	2003		✓	
Mills et al.(9)	2001			✓
Sjogren et al.(10)	2000		✓	
Moulin et al.(11)	1996		✓	
Vaino et al.(12)	1995		✓	
Coda et all.(13)	1994		✓	
Kerr et al.(14)	1991		✓	
Clark et al.(15)	1986			✓
Clark et al.(16)	1986			✓
Saarialho-Kere et al.(17)	1986		✓	
Logsdon et al.(18)	1984	✓		
Redpath et al.(19)	1982		✓	
Pishkin et al.(20)	1980	✓		
Hindmarch et al.(21)	1979	✓		
Tansella et al.(22)	1979	✓		
Ghoneim et al.(23)	1975		✓	
Kortilla et al.(24)	1975		✓	
Kopriva et al.(25)	1974	✓		
Linnoila et al.(26)	1973		✓	
Betts et al.(27)	1972	✓		
Jeffrey et al.(28)	1972			✓
Malpas et al.(29)	1970	✓		
Total number of studies =		7	12	6

The key attributes of each included study are presented in Table 7. With one exception, two different study designs are represented in the overall evidence base for Key Question 2; randomized and non-randomized controlled trials. The exception to this is the study of Sjogren et al.(10), which used a cross-sectional study design.

The study design that was utilized tended to be a function of the aim of the study. If the aim of the study was to examine the acute effects of a drug on performance in healthy, drug-naïve individuals, a randomized controlled trial was used (usually incorporating a crossover). However, if the aim of the study was to investigate the effects of long-term licit drug use on performance, the investigators for ethical reasons tended not to randomize patients to active drug or placebo. Rather they recruited control groups of comparable individuals with the same medical condition who were not taking medication. Study investigators also recruited a normal control group who were used to define what a "normal" outcome measurement is.

Table 7. Key Study Design Characteristics of Studies that Address Key Question 2

Reference	Year	Research question	Drug examined	Study Design	Comparison	Outcomes assessed
OPIOIDS						
Byas-Smith et al.(6)	2005	To determine the effects of long- term stable opioid use on driving performances in patients with chronic pain	Oxycodone and others	Non-randomized controlled trial	21 individuals with chronic pain on opioid treatment compared to 11 individuals with chronic pain not on opioids and 50 healthy volunteers not on opioids.	1. Field driving test in their own car (community drive and obstacle course testing) 2. Office based testing: TOVA and DSST
Sabatowski et al.(8)	2003	To evaluate the effects of long-term opioid treatment on psychomotor and cognitive performance measures	Transdermal fentanyl Median fentanyl: 1.35 ng/ml; Range: 0.53-17.7)	Non-randomized controlled trial	30 chronic non-cancer pain patients on stable doses of fentanyl compared to 90 opioid-free matched healthy controls	1. Test designed to evaluate driving ability in Germany: Sum of the scores of DT, COG and TAVT tests; 2. Motor coordination (2 hand) and VIG
Sjogren et al.(10)	2000	To evaluate the possible influence of long-term oral opioids, pain and reduced heath status on some aspects of psychomotor and cognitive functions in cancer patients.	Morphine and others (oral)	Cross-sectional	Study comparing 5 groups of chronic cancer pain patients: Grp1. KPS A, no pain, no opioid, n = 40 Grp2. KPS B, no pain, no opioid, n = 19 Grp3. KPS B, pain, no opioid, n = 19 Grp4a. KPS B, pain, opioid, n = 31 Grp4b. KPS B, no pain, opioid, n = 21	1. Pain intensity, sedation, opioid side effects 2. Neuropsychological tests: CRT, FTT, and PASAT.
Moulin et al.(11)	1996	Is cognitive function of chronic pain patients affected when placed on opioids?	Morphine Sustained-release (oral) Dosages up to 120 mg daily	RCT (double-blind, placebo controlled with crossover)	61 non-cancer pain patients received morphine and benztropine (active placebo) Washout phase = 2 weeks	1. Pain intensity (VAS and McGill Pain Questionnaire) 2. High Sensitivity Cognitive Screen pre and post placement on chronic opioid treatment (included measure of memory, language, attention and planning) 3. Anxiety and depression (POMS and SCL-90)

Reference	Year	Research question	Drug examined	Study Design	Comparison	Outcomes assessed
Vaino et al(12)	1995	Do cancer patients receiving long-term morphine analgesia show psychomotor impairment vs. patients not on opioids?	Morphine Sustained-release (oral) Mean dose: 209 mg/day	Non-randomized controlled trial	24 cancer patients with pain taking long-term sustained-release oral morphine compared to 25 pain-free cancer patients not taking opioids	1. Computerized test battery designed for professional drivers and industrial operators: (5 psychomotor tests) M30,Q1,LL5, Set 3 and peripheral vision test) 2. Wartegg personality test 3. Neural function tests (body sway(eyes open and closed); finger tapping speeds; simple reaction time for auditory, visual, and associative stimuli; Thermal discrimination (warm and cold)
Coda et al(13)	1993	To assess the magnitudes of cognitive and motor effects of morphine and alfentanil at different steady plasma opioid concentration and examine the relationship between the magnitude of cognitive and motor effects and plasma concentration of the 2 drugs	Morphine and alfentanil (IV) Plasma concentrations for morphine: 20, 40, and 80ng/ml Plasma concentrations for alfentanil: 16,32 and 64 ng/ml	RCT (double-blind, placebo controlled with crossover)	15 healthy male volunteers received each of the following treatments: morphine, alfentanil and saline (placebo) Minimum of 7 days washout period	1. Motor performance: FTT and isometric force 2. Cognitive performance: RSVP 3. Subjective side effects 4. EEG and sedation
Kerr et al.(14)	1991	To evaluate the sensitivity of each cognitive and motor function measure to morphine and examine the relationship between the magnitude of cognitive and motor effects and plasma concentration of morphine	Morphine (IV) Plasma concentrations: 20, 40, and 80 ng/ml	RCT (double-blind, placebo controlled with crossover)	15 healthy male volunteers received morphine and saline (placebo) Minimum of 7 days washout period	1. Motor performance: FTT and isometric force 2. Cognitive performance: RSVP 3. Memory test and visual perception.
Saarialho – Kere et al.(17)	1986	To compare the effects of pentazocine and codeine alone on objective and subjective estimates of performance	Codeine (oral) 100 mg	RCT (double-blind, placebo controlled with crossover)	10 healthy volunteers received pentazocine, codeine, placebo and diazepam at two weeks intervals	1. Objective test: DSST, CFF, Body sway, Maddox wing test, Lateral gaze nystagmus 2. Subjective effects on mood and behavior (VAS)
Redpath et al.(19)	1982	To Compare the respiratory effects of codeine phosphate and glaucine phosphate with regard to intensity and duration of effects	Codeine phosphate (oral) 30 or 60 mg	RCT (double-blind, placebo controlled with crossover)	10 healthy volunteers received each of the following treatments: codeine phosphate, glaucine phosphate or placebo	1. Ventilatory response to CO2, pulse and blood pressure, sedation, time taken to assimilate information was assessed by using the Zahlen-Verbindung Test 2. Cognitive function: DSST
Kortilla et al.(24)	1975	To examine the effects of Meperidine on psychomotor skills related to driving.	Meperidine (IM) 75mg	RCT (double-blind, placebo controlled with crossover)	11 healthy volunteers tested before and after IM injection of saline, diazepam and meperidine	1. Psychomotor tests: reaction time, coordination test, CFF 2. Subjective assessments.

Reference	Year	Research question	Drug examined	Study Design	Comparison	Outcomes assessed
Ghoneim et al.(23)	1975	To what extend does a single dose of fentanyl affect mental and psychomotor functions and how fast is the recovery of these functions?	Fentanyl (IV) 0.1 or 0.2mg	RCT (double-blind, placebo controlled with crossover)	Ten healthy male volunteers received each of the following treatments: fentanyl, diazepam and placebo (at weekly interval)	Psychological tests: Backward digit span, tapping board, serial learning, short term memory, delayed recall, simple reaction time, choice reaction time, visual retention test, subjective rating questionnaire, EEG
Linnoila et al.(26)	1973	To examine the effects of codeine and diazepam , alone and in combination with alcohol on simulated driving test	Codeine phosphate (oral) 50 mg	RCT (double-blind, placebo controlled with crossover)	70 professional drivers from Finnish army were divided into 7 test groups *1) No drug , no drink* *2) placebo capsule, placebo drink* *3) placebo capsule, alcohol* *4) diazepam, placebo drink* *5) diazepam, alcohol* *6) codeine, placebo drink* *7) codein,e alcohol*	1. Driving simulator 2. Subjective assessments
STIMULANTS-Amphetamines and Methylphenidate						
Barkley et al.(5)	2005	To evaluate the effects of two single, acute doses of methylphenidate on the driving performance of adults with ADHD	Methylphenidate (oral) 10 or 20 mg	RCT (double-blind, placebo controlled with crossover)	52 patients diagnosed with ADHD according to DSM-IV diagnostic criteria tested at baseline and after administration of low dose or high dose of MPH or placebo	Driving simulator and continuous performance tests: reaction time, omission errors and commission errors.
Sliber et al.(7)	2005	To examine the acute effects of dexamphetamine on simulated driving performance	Dexamphetamine (oral) 0.42 mg/kg	RCT (double-blind, placebo controlled with crossover)	20 healthy participants tested after administration of dexamphetamine or placebo (1 week apart)	1. Driving simulator (day driving and night driving) 2. Snellen Eye Chart (visual acuity)
Mills et al.(9)	2001	To examine the influence of stimulants on single-target and divided attention responses in different part of the visual field.	Dextroamphetamine (oral) 10 mg	RCT (double-blind, placebo controlled with crossover)	10 healthy volunteers received each of the following treatments: alprazolam, dextroamphetamine and placebo (three day washout periods)	1. POL task (attention test) 2. Subjective assessments
Clark et al.(15)	1986	To examine the effects on auditory selective attention of methylphenidate administered intravenously to normal volunteers	Methylphenidate (IV) 0.65 mg/kg	RCT (double-blind, placebo controlled with crossover)	10 right handed male volunteers received each of the following treatments: methylphenidate, clonidine and placebo (3-7 days washout period)	1. Dichotic monitoring (divided and focused attention) 2. Cardiovascular effects 3. Subjective state.
Clark et al.(16)	1986	To examine the effects on auditory selective attention of methylphenidate and clonidine administered intravenously to normal volunteers	Methylphenidate (IV) 0.65 mg/kg	RCT (double-blind, placebo controlled with crossover)	12 right handed male volunteers received each of the following treatments: methylphenidate, droperidol and placebo	1. Dichotic monitoring (divided and focused attention) 2. Cardiovascular effects 3. Subjective state.

Reference	Year	Research question	Drug examined	Study Design	Comparison	Outcomes assessed
Jeffrey et al.(28)	1972	To manipulate arousal in young and elderly subjects using dextroamphetamine and determine the effects of changes as indicated by GRS and RT	Dextroamphetamine (oral) 5 mg	RCT (double-blind, placebo controlled with crossover)	8 elderly and 10 young subjects received dextroamphetamine and placebo	1. Visual Reaction Time 2. GSR
DEPRESSANTS – BARBITURATES						
Logsdon et al.(18)	1984	To examine acute secobarbital dose treatments effects on choice reaction time in a visual character recognition task	Secobarbital (oral) 2.0 mg/kg or 2.9 mg/kg	RCT (double-blind, placebo controlled with crossover)	18 male college students received each of the following treatments: high dose or medium dose of secobarbital and placebo (at least two days washout period)	Visual Reaction Time and error rates
Pishkin et al.(20)	1980	To examine the effects of barbiturates on several behavior and cognitive tasks	Secobarbital and amobarbital (oral) 200 mg	5 groups, placebo controlled	50 healthy male volunteers received the following treatment: temazepam, flurazepam, barbiturates, placebo and no capsule	1. Simple reaction time 2. Pursuit rotor 3. Speed inference
Tansella et al.(22)	1979	To examine the effects of amylobarbitone sodium and diazepam on simple and complex motor tasks, attention and concentration tasks	Amylobarbitone sodium (oral) Flexible dose	RCT (double-blind, placebo controlled with crossover)	24 newly admitted patients with the primary diagnosis of anxiety neurosis received amylobarbitone sodium, diazepam and placebo	1. Personality assessment 2. Clinical assessment 3. Subjective evaluation 4. Performance measures: DSST, card sorting, simple auditory reaction time, auditory choice reaction time, cancellation tasks, FTT, the symbol coping test, Arithmetic and Gibson spiral maze
Hindmarch et al.(30)	1979	Comparison of the effects of acute nighttime dose of amylobarbitone sodium, nitrazepam, clobazam and placebo on performance measures	Amylobarbitone sodium (oral) 100 mg	RCT (double-blind, placebo controlled with crossover)	20 volunteers received each of the 4 treatments conditions (at weekly intervals): amylobarbitone sodium, nitrazepam, clobazam and placebo	1. Choice reaction time 2. CFF 3. Stabilometer
Kopriva et al.(25)	1974	To examine the effects of pentobarbital on performance in monotonous conditions not prevented by compensatory effort.	Pentobarbital (oral) 150 mg/ 70 kg (oral)	Double-blind, controlled study	90 professional drivers Tested after administration of pentobarbital or placebo	1. Choice reaction time (auditory) 2. qualitative different types of errors were evaluated: errors of omission to discriminate signal and errors of commission

Reference	Year	Research question	Drug examined	Study Design	Comparison	Outcomes assessed
Betts et al.(27)	1972	To determine whether small repeated doses of commonly used tranquilizing drugs affected performances on low speed vehicle handling tests	Amylobarbitone sodium (oral) Five 30 mg doses over 36 hours	double-blind, RCT	100 subjects were divide into 5 groups: 1) amobarbital sodium against placebo 2) double placebo group 3) haloperidol against placebo 4) trifluoperazine against placebo 5) chlordiazepoxide against placebo	1. Vehicle handling test 2. Visual screening test 3. Subjective feeling questionnaire 4. Objective assessment Scale 5. Subjective assessment
Malpas et al.(29)	1970	To examine the effects of amylobarbitone, nitrazepam and placebo in normal healthy young people	Amylobarbitone sodium (oral) 100 or 200 mg	RCT (double-blind, placebo controlled with crossover)	10 healthy male volunteers received amylobarbitone, nitrazepam and placebo	1. Sleep questionnaire 2. Subjective mood Scale 3. Card sorting 4. EEG

CFF = Critical Flicker-Fusion; COG = (Attention test); CRT = Continuous Reaction Time; DSST = Digit Symbol Substitution Test; DT = Determination test; EEG = Electroencephalogram; FTT = Finger Tapping Test; GSR = Galvanic Skin Response; PASAT = Paced Auditory Serial Addition Task; POL = Performance online (Attention test); POMS = Profile of Mood State; RSVP = Rapid Single Visual Presentation; SCL-90 = Symptom Check List-90; TAVT = Test for visual orientation, tachistoscopic perception; TOVA = Test of Variables of Attention; VAS = Visual Analogue Scale; VIG = Vigilance test

Quality of Evidence Base

The results of our assessment of the quality of the studies included in the evidence base for Key Question 2 are presented in Table 8. This assessment found that the quality of the included studies varied in a binomial manner with studies designed to assess the effects of a single acute dose of a Schedule II drug being the highest quality. The studies with the lowest quality scores tended to be long-term follow-up studies. These latter studies tended not to be randomized and were particularly prone to selection bias. In most cases, individuals with the same medical condition were assigned to a study arm based on whether they were taking a particular Schedule II drug or not. Consequently, the patients in the two arms of the study cannot be assumed as being comparable at baseline because there is likely a reason for the difference in their treatment regime.

Most of the randomized controlled trials included in the evidence base for Key Question 2 used a crossover design. In a crossover trial, subjects are randomly allocated to study arms where each arm consists of a sequence of two or more treatments given consecutively. The simplest model is the AB/BA design. Subjects allocated to the AB study arm receive treatment A first, followed by treatment B, and vice versa in the BA arm. Crossover trials allow the response of a subject to treatment A to be contrasted with the same subject's response to treatment B which ensures that differences between patient characteristics across study arms is not a factor. Removing patient variation in this way makes crossover trials potentially more efficient than similar sized, parallel group trials in which each subject is exposed to only one treatment. In theory treatment effects can be estimated with greater precision given the same number of subjects.

The principal drawback of the crossover design is that the effects of one treatment may "carry over" and alter the response to subsequent treatments. The usual approach to preventing this is to introduce a washout (no treatment) period between consecutive treatments. This washout period must be long enough to allow the effects of a treatment to wear off. A variation on this is to restrict outcome measurement to the latter part of

each treatment period. Most of the crossover studies included in the evidence base were protected from "carry over" bias.

Table 8. Quality of the studies that Assess Key Question 2

Reference	Year	Quality Scale Used (see Appendix F)	Quality Score	Quality
Studies of Schedule II Opioids				
Byas-Smith et al.(6)	2005	ECRI Quality Scale I-Comparative Trials	4.0	Low
Sabatowski et al.(8)	2003	ECRI Quality Scale I-Comparative Trials	4.2	Low
Sjogren et al.(10)	2000	ECRI Quality Scale I-Comparative Trials	5.0	Low
Moulin et al.(11)	1996	ECRI Quality Scale II-Comparative Trials (with crossover)	6.0	Moderate
Vaino et al(12)	1995	ECRI Quality Scale I-Comparative Trials	4.8	Low
Coda et al(13)	1993	ECRI Quality Scale II-Comparative Trials (with crossover)	8.4	High
Kerr et al.(14)	1991	ECRI Quality Scale II-Comparative Trials (with crossover)	8.0	High
Saarialho-Kere et al.(17)	1986	ECRI Quality Scale II-Comparative Trials (with crossover)	9.0	High
Redpath et al.(19)	1982	ECRI Quality Scale II-Comparative Trials (with crossover)	8.0	High
Kortilla et al.(24)	1975	ECRI Quality Scale II-Comparative Trials (with crossover)	8.6	High
Ghoneim et al.(23)	1975	ECRI Quality Scale II-Comparative Trials (with crossover)	8.8	High
Linnoila et al.(26)	1973	ECRI Quality Scale I-Comparative Trials	4.8	Low
Studies of Schedule II Stimulants				
Barkley et al.(5)	2005	ECRI Quality Scale II-Comparative Trials (with crossover)	8.4	High
Sliber et al.(7)	2005	ECRI Quality Scale II-Comparative Trials (with crossover)	8.2	High
Mills et al.(9)	2001	ECRI Quality Scale II-Comparative Trials (with crossover)	8.5	High
Clark et al.(15)	1986	ECRI Quality Scale II-Comparative Trials (with crossover)	8.8	High
Clark et al.(16)	1986	ECRI Quality Scale II-Comparative Trials (with crossover)	7.9	Moderate
Jeffrey et al.(28)	1972	ECRI Quality Scale II-Comparative Trials (with crossover)	6.4	Moderate
Studies of Schedule II Depressants				
Logsdon et al.(18)	1984	ECRI Quality Scale II-Comparative Trials (with crossover)	8.6	High
Pishkin et al.(20)	1980	ECRI Quality Scale I-Comparative Trials	4.2	Low
Tansella et al.(22)	1979	ECRI Quality Scale II-Comparative Trials (with crossover)	8.6	High
Hindmarch et al.(30)	1979	ECRI Quality Scale II-Comparative Trials (with crossover)	7.9	Moderate

Reference	Year	Quality Scale Used (see Appendix F)	Quality Score	Quality
Kopriva et al.(25)	1974	ECRI Quality Scale I-Comparative Trials	5.4	Low
Betts et al.(27)	1972	ECRI Quality Scale I-Comparative Trials	6.7	Moderate
Malpas et al.(29)	1970	ECRI Quality Scale II-Comparative Trials (with crossover)	8.6	High

Generalizability of Evidence to Target Population

Important characteristics of the individuals included in the studies that form the three evidence bases for Key Question 2 are presented in Table 9. The information included in this table demonstrates that currently available data that is directly generalizable to CMV drivers is extremely scarce; only two of the 25 included studies enrolled individuals who might be considered to be comparable to CMV drivers in the United States.(25,26)

Linnoila et al.(26) evaluated the effects of the Schedule II opioid codeine phosphate on simulated driving in a group of "professional drivers" recruited from the Finnish army. Similarly, Kopriva et al.(25) examined the effects of the barbiturate pentobarbital on cognitive and psychomotor performance in a group of "professional drivers." Unfortunately, it is not clear from the details of either study what criteria the authors used to define a "professional driver." Consequently, it remains a possibility that none or a small proportion of the enrollees in these two studies actually drove large trucks or buses.

Other factors that may limit the generalizability of the findings of the studies included in this section of the evidence report are the following:

- The proportion of women enrolled in many of the included studies is higher than the prevalence of female CMV drivers.
- Studies that were designed to examine the acute effects of a Schedule II drug tended to recruit young, healthy individuals. CMV drivers in the United States tend to be older and often have a number of medical conditions, including cardiovascular disease, diabetes mellitus, and obesity.

Table 9. Individuals Enrolled in Studies that Address Key Question 2

Reference	Year	Treatment Group	Age distribution	Disease state	Pain level	Length of education	%Male	%White	Driving experience	Generalizability to CMV drivers
Schedule II opioids										
Byas-Smith et al.(6)	2005	n = 21 (Opioid)	Mean: 47.7 (SD: 10.9) years	Chronic pain	Mean 45.8 (SD: 24) VAS	Mean 14 (SD: 3) years	47%	NR	Mean 31.3 (SD: 11.5) years	Unclear
		n = 11 (Other analgesics)	Mean 46.5 (SD: 6.9) years	Chronic pain	Mean 40 (SD: 21) VAS	Mean: 15 (SD: 2.6) years	45%	NR	Mean: 28.9 (SD: 5.9) years	
		n = 50 Controls	Mean: 42.6 (SD: 9.1) years	Healthy	Mean 4.9 (SD: 13.9) VAS	Mean 16.6 (SD: 3.4) years	46%	NR	Mean: 21.9 (SD: 11.8) years	
Sabatowski et al.(8)	2003	n = 30 (Opioid)	Mean 50.0 (SD: 9) years (Rng: 34-65)	Chronic pain	Mean: 3 (Rng: 0-8) VAS	NR	60%	NR	10,000 (Rng: 500-60,000)	Unclear
		n = 90 (Controls)	Mean: 50.0 (SD: 9) years (Rng: 34-65)	Healthy	No pain	NR	63%	NR	NR	
Sjogren et al.(10)	200	n = 31 (Opioid)	Median: 59.0 (Rng: 47-74) years	Cancer	Median 35 (Rng: 2-88) VAS	NR	68%	NR	NR	Unclear
		n = 21 (Opioid)	Median: 60.0 (Rng; 46-73) years	Cancer	No pain	NR	57%	NR	NR	
		n = 40 (no pain, no opioid)	Median; 62.5 (Rng: 49-73) years	Cancer	No pain	NR	47.5%	NR	NR	
		n = 19 (pain, no opioid)	Median 63.0 (Rng: 40-75) years	Cancer	Median: 24 (Rng:10-93) VAS	NR	80%	NR	NR	
		n = 19 (no pain, no opioid)	Median: 58.0 (Rng: 46-76) years	Cancer	No pain	NR	68%	NR	NR	
Moulin et al.(11)	1996	n = 61 (Crossover-opioid and benztropine [active placebo])	Mean: 40.4 (Rng: 26-67) years	Chronic pain	Mean: 44.1 (Rng: 14-65) PDI	Mean: 12.9 (Rng: 8-19) years	41%	NR	NR	Unclear
Vaino et al.(12)	1995	n = 24 (Opioid)	Mean: 53.0 (SD: 9.4) years	Cancer	NR	Mean: 11 years (Basic education)	50%	NR	NR	Unclear
		n = 25 (Controls)	Mean: 51.0 (SD: 11.2) years	Cancer	NR	Mean : 12 years (Basic education)	40%	NR	NR	

Reference	Year	Treatment Group	Age distribution	Disease state	Pain level	Length of education	%Male	%White	Driving experience	Generalizability to CMV drivers
Coda et al.(13)	1993	n = 15 (Crossover-opioid and placebo)	Rng: 21–37 years	Healthy	No pain	NR	100%	NR	NR	Unclear
Kerr et al.(14)	1991	n = 15 (Crossover-opioid and placebo)	Rng: 21–37 years	Healthy	No pain	NR	100%	NR	NR	Unclear
Saarialho-Kere et al(17)	1986	N = 10 (Crossover - opioid, pentazocine, diazepam and placebo)	Rng: 20–26 years	Healthy	No Pain	(Student volunteers)	50%	NR	NR	Unclear
Redpath et al.(19)	1982	n = 10 (Crossover-opioid, glaucine phosphate and placebo)	Rng: 23–36 years	Healthy	No pain	NR	60%	NR	NR	Unclear
Kortilla et al.(24)	1975	n = 11 (Crossover-opioid, diazepam and placebo)	Mean: 25.0 (SD: 2.6) years	Healthy	No pain	(Student volunteers)	73%	NR	NR	Unclear
Ghoneim et al.(23)	1975	n = 10 (Crossover-opioid, diazepam, and placebo)	Mean: 22.9 (SD: 1.5) years	Healthy	No pain	NR	100%	NR	NR	Unclear
Linnoila et al.(26)	1973	n = 10 Opioid n = 10 No drug n = 10 Placebo	Rng: 19–22	Healthy	No pain	NR	NR	NR	Young professional drivers in compulsory service in motorized troops (Finnish army)	Fair/Poor?
Stimulants-Amphetamines and Methylphenidate										
Barkley et al.(5)	2005	n = 52 (Crossover-Stimulant and placebo)	Mean: 31.3 (SD: 11.3) years	ADHD	NA	Mean: 14 (SD: 2.2) years Mean IQ: 104.7 (SD:9.7)	74%	83.3%	Mean exposure: 252 (SD: 203) miles/week Mean years of driving experience: 14.5 (SD: 11.1)	Unclear
Sliber et al.(7)	2005	n = 20 (Crossover-Stimulant and placebo)	Mean: 25.4 (SD: 3.3) years	Healthy	NA	Min. years of education: 11	50%	NR	Had at least 3 years of driving experience	Unclear
Mills et al.(9)	2001	n = 18 (Crossover-Stimulant, sedative	Mean: 29.9 (Range: 19-37)	NR	NA	NR	22.8%	77.8%	NR	Unclear

Reference	Year	Treatment Group	Age distribution	Disease state	Pain level	Length of education	%Male	%White	Driving experience	Generalizability to CMV drivers
		and placebo)	years							
Clark et al.(15)	1986	n = 10 (Crossover-Stimulant, clonidine and placebo)	Range: 18-30 years	Screened for medical and psychiatric abnormalities and for hearing deficits	NA	NR	100%	NR	NR	Unclear
Clark et al.(16)	1986	n = 12 (Crossover-Stimulant, droperidol and placebo)	Range: 18-30 years	Screened for medical and psychiatric abnormalities and for hearing deficits	NA	NR	100%	NR	NR	Unclear
Jeffrey et al.(28)	1972	n = 8 Elderly n = 10 Young (Crossover-Stimulant and placebo)	Mean: 70.5 (Range: 66–78) years Mean: 22.9 (Range: 21–33) years	All were medically screened	NA	NR	NR	NR	NR	Unclear
Schedule II depressants										
Logsdon et al.(18)	1984	n = 18 (Crossover-Barbiturate and placebo)	Range: 21–35	NR	NA	(College students)	100%	NR	NR	Unclear
Pishkin et al.(20)	1980	n = 10 Barbiturate n = 10 Placebo n = 10 No drug	Range: 21–30 years	NR	NA	(College students)	100%	NR	NR	Unclear
Tansella et al.(22)	1979	n = 24 (Crossover Barbiturate, diazepam, and placebo)	Mean: 41.7 (SD: 8.7) (Range: 29–60) years	Newly admitted patients with anxiety neurosis	NA	Mean: 5 (SD: 1) years (Most of the patients were from the lower social class)	25%	NR	NR	Unclear
Hindmarch et al.(30)]	1979	n = 20 (Crossover-Barbiturate, nitrazepam,	Mean: 28 years	NR	NA	NR	50%	NR	NR	Unclear

Reference	Year	Treatment Group	Age distribution	Disease state	Pain level	Length of education	%Male	%White	Driving experience	Generalizability to CMV drivers
		clobazam and placebo)								
Kopriva et al.(25)	1974	n = 90 (number of subjects in each group not reported)	NR	NR	NA	NR	NR	NR	Professional drivers	Fair/Poor?
Betts et al.(27)	1972	n = 20 Barbiturate/placebo n = 20 Placebo/placebo	NR	NR	NA	NR	50%	NR	Men had significantly more driving experience (2% level), had driven significantly more miles (1% level), and had significantly more driving convictions (2% level) than women drivers.	Unclear
Malpas et al.(29)	1970	N = 10 (Crossover-barbiturate, nitrazepam and placebo)	Range: 18–20 years	Healthy	NA	Volunteer Medical students	100%	NR	NR	Unclear

NA = Not applicable; NR = Not reported

Findings

As stated previously, Schedule II drugs generally fall into one of three drug classes; stimulants, depressants, and opioids. Because both the mechanism of action and medical indications for each of these three drug classes differ considerably from one another, we present the results of our assessment of the evidence pertaining to each drug class separately.

Opioids

A total of 12 included studies evaluated the effects of Schedule II opioids on one of the indirect measures of driving ability considered in this evidence report (Table 10). Of these 12 studies, two examined the effects of opioids on experimental or simulated driving ability, 11 examined the effects of opioids on cognitive and/or psychomotor function, and two examined the effects of opioids on mood or behavior.

Table 10. Relevant Outcomes Addressed by Opioid Studies

Reference	Year	Experimental/Simulated Driving Ability	Motor and/ or Cognitive Performances	Mood* or Behavior†
Byas-Smith et al.(6)	2005	√‡	√	
Sabatowski et al.(8)	2003		√	
Sjogren et al.(10)	2000		√	
Moulin et al.(11)	1996		√	√
Vaino et al.(12)	1995		√	√
Coda et al.(13)	1993		√	
Kerr et al.(14)	1991		√	
Saarialho-Kere et al.(17)	1986		√	
Redpath et al.(19)	1982		√	
Kortilla et al.(24)	1975		√	
Ghoneim et al.(23)	1975		√	
Linnoila et al.(26)	1973	√		
Total number of studies =		**2**	**11**	**2**

* Mood: Objective and subjective mood scales; Subjective Assessments: Sedation assessed using visual analogue scale (SVAS) or questionnaire and perception of performance

† Behavior: Distractibility, difficulty in following direction, impulsivity, inattention, mental slowness, talkative

‡ On-Road Driving: Patients evaluated while driving their own automobile and Vehicle-Handling Test (parking test, gap estimation, weaving test). All subjects used the same vehicle

Experimental/Simulated Driving Ability

As stated above, two included studies examined the effects of an opioid on simulated or experimental driving ability(6,26). Although both studies evaluated the effects of Schedule II opioids on simulated or experimental driving ability, the aims of the two studies were quite different. Linnoila et al.(26) investigated the effects of a single dose of an opioid on the driving ability of young healthy opioid-naïve individuals. The purpose of the study of Byas-Smith et al.,(6) on the other hand, was to examine the effects of opioids on driving ability in a group of individuals with chronic non-malignant pain (>3 months) who had been taking stable doses of opioid for at least one week prior to testing. The former study provides information on the effect of a therapeutic dose of opioids on driving ability that one might expect to see among opioid-naïve individuals who are taking the drug for the first time. The latter study provides information on the long-term effects of opioids on driving ability in a group of individuals who would be considered as licit opioid users; individuals with chronic pain.

Effect of Opioids on Driving Ability among Opioid-Naive Individuals

Linnoila et al. examined the effects of a single 50 mg dose of codeine on simulated driving ability using a parallel arm controlled trial (Quality Score: 4.8; Low Quality)[9]. Seventy young (19 to 22 years), healthy professional drivers from the Finnish army were assigned to one of seven treatment arms. One of these arms received codeine alone (n = 10) and another arm received placebo (n = 10). Driving ability was tested 30 minutes following drug administration using a modified simulator (Sim-L-Car), which took approximately 40 minutes to compete.

A single 50 mg oral dose of codeine had a significant deleterious effect on driving ability in this study. Individuals in the codeine arm of the study experienced more collisions than those in the placebo group (P <0.001). In addition, individuals in the codeine group drove off the simulated road an average of three times during the 40 minute session; whereas, nobody in the placebo arm of the study drove off the road at all.

Effect of Opioids on Driving Ability among Licit Long-Term Opioid Users

Byas-Smith et al. recruited 32 individuals with chronic pain and 50 healthy individuals into a non-randomized controlled trial (Quality Score: 4.0; Low Quality). Individuals with chronic pain were divided into two study arms defined by whether an individual was taking a stable dose of opioid (n = 21) or not (n = 11) at the time of recruitment. The driving ability of the group individuals who were on long-term, stable doses of opioid was then compared to that of the group of individuals with chronic pain not taking opioids and the group of healthy individuals. Driving ability was tested while enrollees drove their own car through a planned route in the community and on a five-station obstacle course.

No significant differences were observed among the three groups in driving performance on either the community driving course or the obstacle course. Thus, the findings of this study do not support the contention that long-term use of opioids for a licit purpose has a deleterious impact on driving ability.

[9] Poor reporting precludes one from determining whether this study was randomized and whether the study was protected from selection bias.

Table 11. Driving Ability Following Opioid Administration

Reference	Year	Opioid (Dose + mode of administration)	Treatment Groups	Type of Test	Measure of performance	Outcome		Interpretation of Results
Byas-Smith et al.(6)	2005	Various opioids	Morphine + pain grp. Vs. No morphine + pain grp. Vs. No morphine + no pain grp.	Community drive*		Opioid vs non-opioid	Opioid vs normals	No evidence that driving ability of individuals with chronic non-malignant pain taking long-term, stable dose opioids is impaired when compared with a group of individuals with chronic pain not taking opioids and a group of normals with no pain.
					Speeding violations:			
					Total number	NS	NS	
					Duration	NS	NS	
					Turning violations:			
					Driving on curb	NS	NS	
					Crossing center line	NS	NS	
					Failure to signal	NS	NS	
					Stopping violations:			
					Sudden stopping	NS	NS	
					Failure to stop at lights or stop sign	NS	NS	
					Lane violations:			
					Crossing center lane while not turning	NS	NS	
					Swerving within lane	NS	NS	
				Obstacle course†	*Parallel parking*:			
					Time to complete station	NS	NS	
					Number of cone touches	NS	NS	
					Number of cones run over	NS	NS	
					Discrepancy from optimal curb distance			
					Front tire	NS	NS	
					Rear tire	NS	NS	
					Circle drive:			
					Time to complete station	NS	NS	
					Number of cone touches	NS	NS	
					Number of cones run over	NS	NS	
					Barrier drive:			
					Time to complete station	NS	NS	
					Reverse driving:			
					Time to complete station	NS	NS	
					Number of cone touches	NS	NS	
					Number of cones run over	NS	NS	
					Forward drive:			
					Time to complete station	NS	NS	
					Number of cone touches	NS	NS	
					Number of cones run over	NS	NS	

Reference	Year	Opioid (Dose + mode of administration)	Treatment Groups	Type of Test	Measure of performance	Outcome	Interpretation of Results
Linnoila et al.(26)	1973			Modified sim-L car operated by a shadow projection of a point source of light	*Electrical Recordings* Steering wheel reversals Number of times brakes applied Number of times clutch applied Number of times turning signal used Continuous recording of speed Continuous recording of gear shifting Brake reaction time Pulse frequencies *Recordings from TV monitor* Number of neglected instructions Number of collisions Driving off road	 Less in codeine grp ($p < 0.05$) NR NR NR NR NR NR Reduced in codeine grp ($P < 0.01$) NR Increased in codeine grp ($P < 0.001$) 3 drivers in codeine grp drove off road compared to none in control grp	A single 50 mg dose of codeine had a deleterious effect on some aspects of driving ability among young professional drivers.

* Consisted of a fixed route driven in test subjects own vehicle; 7 miles urban and 4 miles interstate driving. Individuals instructed not to exceed posted speed limits by >5 mph. Individuals vehicle trailed by an investigator in another car who videotaped community drive and kept a record of subjects speed, etc. †Adaptation of Georgia State precision driving course

NS = No significant drug effect; NR = Not reported.

Cognitive and/or Psychomotor Function

Eleven included studies assessed the effects of an opioid on cognitive and/or psychomotor function. These 11 studies utilized a total of 32 different psychometric tests with very little overlap in the tests that were used (Table 12). Only the Finger Tapping Test (FTT) and the Digit Symbol Substitution Test (DSST) were utilized by three or more studies. Performing a meta-analysis of data from these two instruments alone cannot be justified because they represent the findings of only a very small proportion of available studies (FTT-33% and DSST-25% of studies). Consequently, our assessment of the findings of the 11 included studies is limited to a qualitative evaluation of the available evidence.

Table 12. Measures of Cognitive and Psychomotor Function Used in Opioid Studies

Outcome assessed	Byas-Smith et al.(6) (2005)	Sabatowski et al.(8) (2003)	Sjogren et al.(10) (2000)	Moulin et al.(11) (1996)	Vaino et al.(12) (1995)	Coda et al.(13) (1993)	Kerr et al.(14) (1991)	Saarialho-Kere et al.(17) (1986)	Redpath et al.(19) (1982)	Kortilla et al.(24) (1975)	Ghoneim et al.(23) (1975)	Total number of studies
FTT			√		√	√	√					4
DSST	√							√	√			3
CFF								√		√		2
Choice Reaction Time (visual)										√	√	2
Isometric force						√	√					2
RSVP						√	√					2
Simple reaction time (Visual)					√						√	2
Backward Digit Span											√	1
Choice reaction time (Auditory)										√		1
COG		√										1
Cognitive* screen				√								1
Continuous reaction time (Auditory)			√									1
Coordination (2-hand)		√										1
Coordination test (NS)										√		1
Delayed recall											√	1
DT		√										1
LL5					√							1
M30					√							1
Memory test (NS)							√					1
PASAT			√									1
Q1					√							1
Serial learning											√	1
SET 3					√							1

Outcome assessed	Byas-Smith et al.(6) (2005)	Sabatowski et al.(8) (2003)	Sjogren et al.(10) (2000)	Moulin et al.(11) (1996)	Vaino et al.(12) (1995)	Coda et al.(13) (1993)	Kerr et al.(14) (1991)	Saarialho-Kere et al.(17) (1986)	Redpath et al.(19) (1982)	Kortilla et al.(24) (1975)	Ghoneim et al.(23) (1975)	Total number of studies
Short term memory											√	1
Simple reaction time (Associative)					√							1
Simple reaction time (Auditory)					√							1
Tapping board											√	1
TAVT		√										1
TOVA	√											1
VIG		√										1
Visual retention test											√	1
Zahlen-Verbindung test †									√			1

*High Sensitivity Cognitive Screen (includes measures of memory, language, attention, and planning); †Time to assimilate information test

CFF = Critical Flicker-Fusion; COG = (Attention test); DSST = Digit Symbol Substitution Test; DT = Determination test; FTT = Finger Tapping Test; NS = Not specified; PASAT = Paced Auditory Serial Addition Task; ROCFT = Rey-Osterreith Complex Figure Test; RSVP = Rapid Single Visual Presentation; TAVT = Test for visual orientation, tachistoscopic perception; TOVA = Test of Variables of Attention; VIG = Vigilance test

The findings of the 11 included studies that investigated the effects of opioids on cognitive and/or psychometric function are presented in Table 13. For the reasons provided above we subdivided the evidence base into two smaller evidence bases: an evidence base comprised of studies that examined cognitive and/or psychomotor function following administration of a single dose of an opioid to an opioid-naïve individual (k = 6); and an evidence base comprised of studies that examined cognitive and/or psychomotor function among long-term opioid users (k = 5).

Effect of Opioids on Driving Ability among Opioid-Naive Individuals

Six studies (Overall Quality Score = 8.5; High) assessed the effects of administration of an opioid on cognitive and psychomotor function among opioid-naïve healthy individuals. The findings of the six studies were inconsistent. Four of the six studies found that psychomotor and high level (but not low level) cognitive function were adversely affected by a single dose of an opioid (morphine, alfentanil, meperidine, or fentanyl). The remaining two studies, both of which evaluated the effects of codeine, found no evidence that psychomotor or cognitive function was impaired among codeine-naïve individuals following administration of a single dose (30, 60, or 100 mg) of the opioid. Whether this inconsistency in the findings of the six studies included in this assessment is a consequence of differences in the drugs themselves, in drug dosage, in measurement timing, in the sensitivity of the psychometric instruments used to evaluate cognitive and psychomotor function, in the size of the included studies, or in the characteristics of the individuals enrolled in the studies cannot be determined at this time.

Effect of Opioids on Driving Ability among Licit Long-Term Opioid Users

Five studies (Overall Quality Score = 4.8; Low) assessed the effects of the long-term administration of an opioid on cognitive and psychomotor function among individuals with chronic pain. Two of the five included studies provide limited evidence to support

the contention that long-term opioid use for a licit purpose has a deleterious impact on cognitive or psychomotor function. Sabatowski et al.(8) found that individuals with chronic nonmalignant pain treated with transdermal fentanyl (25 to 400 µg/hour) showed deficits in a number of measures of cognitive and psychomotor function. However, the z-transformed sum score that included data from all of the tests performed combined was not found to be statistically significant. Moulin et al.(11) demonstrated that individuals with non-malignant pain who were treated with oral sustained release morphine (60 mg b.i.d) demonstrated deficits in memory. However, none of the remaining measures of cognitive function that these investigators assessed were found to be deleteriously impacted.

Table 13. Cognitive and Psychomotor Function Following Opioid Administration

Reference	Year	Opioid (Dose + mode of admin.)	Treatment Groups	Test	Findings	Conclusion
Studies of Effects of Single doses of Opioids in Opioid-Naive Individuals						
Coda et al.(13)	1993	Morphine Plasma concentration Low = 20 ng/ml Medium = 40 ng/ml High = 80 ng/ml (upper limit of therapeutic range = 100 ng/ml)	Morphine-naïve healthy individuals + morphine (3 different doses) Vs. Morphine-naïve healthy individuals + placebo	Motor Function Tests Finger tapping Preferred hand Non-preferred hand Bimanual Isometric force measures Maintenance of low constant force with visual feedback Maintenance of low constant force without visual feedback	 *P* = NS *P* = NS *P* = NS *P* <0.05§ *P* <0.05§	Morphine did not affect simple motor function. Morphine has a significant dose dependant deleterious impact on some aspects of cognitive and psychomotor function of morphine naïve normal individuals. Morphine increased time needed to comprehend language. Limited ability to maintain low levels of force. Performance deficit greater without visual feedback
				Verbal comprehension and memory RSVP Reading speed	 *P* <0.05§	
		Alfentanil Plasma concentration Low = 16 ng/ml Medium = 32 ng/ml High = 64 ng/ml (upper limit of therapeutic range = 100 ng/ml)	Alfentanil-naïve healthy individuals + alfentanil (3 different doses) Vs. Alfentanil-naïve healthy individuals + placebo	Motor Function Tests Finger tapping Preferred hand Non-preferred hand Bimanual Isometric force measures Maintenance of low constant force with visual feedback Maintenance of low constant force without visual feedback	 *P* = NS *P* = NS *P* = NS *P* <0.05§ *P* <0.05§	Alfentanil did not affect simple motor function. Alfentanil has a significant dose dependant deleterious impact on some aspects of cognitive and psychomotor function of morphine naïve normal individuals. Alfentanil increased time needed to comprehend language. Limited ability to maintain low levels of force. Performance deficit greater without visual feedback
				Verbal comprehension and memory RSVP Reading speed	 *P* <0.05§	

Reference	Year	Opioid (Dose + mode of admin.)	Treatment Groups	Test	Findings	Conclusion
Kerr et al.(14)	1991	Morphine Plasma concentration Low = 20 ng/ml Medium = 40 ng/ml High = 80 ng/ml (upper limit of therapeutic range = 100 ng/ml)	Morphine-naïve healthy individuals + morphine (3 different doses) Vs. Morphine-naïve healthy individuals + placebo	Motor Function Tests Finger tapping Preferred hand Non-preferred hand Bimanual Isometric force measures Maximum force Maintenance of low constant force with visual feedback Maintenance of low constant force without visual feedback Fast repetitive changes in force Ability to attain a target force	 *P* = NS *P* = NS *P* = NS *P* = NS *P* <0.05 (high dose only)§ *P* <0.05 (high dose only)§ *P* = NS *P* <0.05 (high dose only)§	Morphine did not affect simple motor function Morphine has a significant dose dependant deleterious impact on some aspects of cognitive and psychomotor function of morphine naïve normal individuals. Morphine increased time needed to comprehend language. Limited ability to maintain low levels of force. Performance deficit greater without visual feedback.
				Verbal comprehension and memory RSVP Reading time Answers to questions	 *P* <0.05 (medium and high dose) § P = NS	
Saarialho-Kere et al.(17)	1986	Oral codeine (100 mg)	Codeine-naïve healthy individuals + codeine Vs. Codeine-naïve healthy individuals + placebo	DSST	*P* = NS	No evidence that oral codeine has an impact on cognitive function when given in a single oral dose of 100 mg
Redpath et al.(19)	1982	Codeine (30 and 60 mg)	Codeine-naïve healthy individuals + codeine Vs. Codeine-naïve healthy individuals + placebo	DSST Zahlen-Verbindung Test	*P* = NS *P* = NS	No evidence that codeine has an impact on cognitive function when given in a single oral dose of 30 or 60 mg.

Reference	Year	Opioid (Dose + mode of admin.)	Treatment Groups	Test	Findings	Conclusion
Kortilla et al.(24)	1975	Meperidine (Single Injection: 75 mg)	Meperidine-naïve healthy individuals + meperidine Vs. Meperidine-naïve healthy individuals + placebo	Reactive skills Cumulative reaction time % mistakes Coordination skills Coordination test 1 Mistake % Driving time	 *P* <0.01§ P = NS *P* <0.01§ *P* <0.05§ P = NS	A single 75 mg intramuscular injection of meperidine had a significant deleterious impact on cognitive and psychomotor performance in meperidine naïve individuals. This effect persisted for >12 hours. Two subjects experienced syncope after administration of meperidine.
Ghoneim et al.(23)	1975	Fentanyl (single dose 0.1 or 0.2 mg)	Fentanyl-naïve healthy individuals + Fentanyl Vs. Fentanyl-naïve healthy individuals + placebo	Backward digit span 0.1 mg fentanyl 0.2 mg fentanyl	 P = NS P <0.05 (at 2 hours)§	A single, high (but not low) dose of fentanyl had a significant effect on some aspects of psychomotor and cognitive function in fentanyl naïve normal individuals. This deleterious effect diminished to pretreatment levels by 8 hours.
				Tapping board 0.1 mg fentanyl 0.2 mg fentanyl	 P = NS P <0.05 (at 2 hours)§	
				Serial learning 0.1 mg fentanyl 0.2 mg fentanyl	 P = NS P = NS	
				Short-term memory 0.1 mg fentanyl 0.2 mg fentanyl	 P = NS P = NS	
				Delayed recall 0.1 mg fentanyl 0.2 mg fentanyl	 P = NS P = NS	
				Simple reaction time 0.1 mg fentanyl 0.2 mg fentanyl	 P = NS P = NS	
				Choice reaction time 0.1 mg fentanyl 0.2 mg fentanyl	 P = NS P = NS	
				Visual retention test 0.1 mg fentanyl 0.2 mg fentanyl	 P = NS P = NS	

Reference	Year	Opioid (Dose + mode of admin.)	Treatment Groups	Test	Findings	Conclusion
Studies of Chronic Opioid Use						
Byas-Smith et al.(6)	2005	Various opioids	Morphine + pain grp. Vs. No morphine + pain grp. Vs. No morphine + no pain grp.	TOVA (Vs. no morphine) Reaction time (msec) Errors of omission Errors of commission	 *P* = NS *P* = NS *P* = NS	Individuals with chronic non-malignant pain taking stable doses of morphine for more than 1 week do not demonstrate significant reductions in cognitive or psychomotor function.
				TOVA (Vs. normal controls) Reaction time (msec) Errors of omission Errors of commission	 *P* = NS *P* = NS *P* = NS	
				DSST (score) Vs. no morphine DSST (score) Vs. normal controls	*P* = NS *P* = NS	
Sabatowski et al.(8)	2003	Transdermal fentanyl (25 to 400 µg/hour)*	Individuals with chronic non-malignant pain Vs. Historical normal control group	*Sum Score (z-transformed DT, COG and TAVT scores)*†	*P* = 0.38‡§	Individuals with chronic non-malignant pain who have been taking stable doses of fentanyl for more than 12 days do demonstrate some reductions in cognitive and/or psychomotor function.
				COG† Wrong answers (n) Correct answers (n) MRT (sec) Score	 *P* = NS *P* >0.05‡§ *P* >0.05‡§ *P* >0.05‡§	
				DT† Processed items (n) Wrong reactions (n) Correct reactions (n) MRT (sec)/Score	 *P* = NS *P* = NS *P* >0.05‡§ *P* >0.05‡§	
				TAVT† Processing time (sec) Wrong answers (n)/Score	 *P* = NS *P* >0.05‡§	
				2-Hand† Mean time (sec) Time off track (%) Score	 *P* >0.05‡§ *P* >0.05‡§ *P* >0.05‡§	
				VIG† Wrong answers (n) MRT (sec) Score	 *P* >0.05‡§ *P* >0.05‡§ *P* >0.05‡§	

Reference	Year	Opioid (Dose + mode of admin.)	Treatment Groups	Test	Findings	Conclusion
Sjogren et al.(10)	2000	Various oral opioids (NR)	Cancer patients on opioids for pain Vs. Cancer patients not on opioids	Continuous reaction time		The use of long-term opioids in patients with cancer did not in and of itself have a deleterious effect on cognitive or psychomotor function. The presence of cancer, however, when associated with a reduction in performance status (Karnovsky score) seems to have a deleterious effect on some aspects of cognitive and psychomotor function.
				Finger tapping test		
				Paced auditory serial addition task		
Moulin et al.(11)	1996	Oral sustained release morphine (60 mg b.i.d)	Individuals with chronic non-malignant pain + morphine Vs. Individuals with chronic non-malignant pain + active placebo	High sensitivity cognitive screen		Individuals with chronic non-malignant pain receiving taking stable doses of morphine for 9 weeks do not demonstrate reductions in cognitive function. The exception to this was memory.
				Overall score	*P* = NS	
				Memory	*P* = 0.04§	
				Language	*P* = NS	
				Attention and concentration	*P* = NS	
				Self-planning and regulation	*P* = NS	
Vaino et al.(12)	1995	Slow-release oral morphine (50 to 1100 mg/day)*	Cancer patients on morphine Vs. Cancer patients not on morphine	M 30: Matrices for nonverbal basic intelligence		Morphine has little effect on cognitive and psychomotor functions related to driving ability in patients with cancer.
				No. correct answers	*P* = 0.956	
				No of wrong answers	*P* = 0.245	
				Q1 Test of capacity for attention		
				Fluctuation in items processed	*P* = 0.417	
				LL5: Concentration and structuring ability		
				Items processed /45 items	*P* = 0.186	
				Number of errors	*P* = 0.711	
				SET 3: Fluency of motor reactions		
				Time used (s)	P = 0.343	
				Number of errors	*P* = 0.285	
				Finger tapping/15 sec	*P* = 0.023 (morphine grp superior)	
				Auditory reaction time (ms)	*P* = 0.289	
				Visual reaction time (ms)	*P* = 0.497	
				Associative reaction time (ms)	*P* = 0.930	

*Dose stable for at least 2 weeks prior to study; †Per-protocol population with nine subjects who were found to be taking drugs excluded by protocol removed; ‡Not significantly non-inferior; §opioid shows deterioration in function when compared to control

DSST = Digit symbol substitution test; MRT = Mean reaction time; NS = No significant adverse drug effect; TOVA = Test of variables of attention.

Mood and Behavior

Two included studies (Overall Quality Score: 5.4; Low) examined the effects of an opioid on mood and/or behavior. Both included studies examined the effects of long-term morphine use on mood or behavior among individuals with chronic pain. The findings of these two included studies as they pertain to these outcomes are presented in Table 14. Neither study provided any evidence to support the contention that the long-term use of morphine for a licit purpose has a negative impact on mood or behavior.

Table 14. Mood and Behavior Following Opioid Administration

Reference	Year	Opioid (Dose + mode of administration)	Treatment Groups	Test Used	Findings	Conclusion
Moulin et al.(11)	1996	Oral sustained release morphine (60 mg b.i.d)	Individuals with chronic non-malignant pain + morphine Vs. Individuals with chronic non-malignant pain + active placebo	Profile of Mood States Symptom Checklist Total Score Somatization Depression Anxiety Hostility	NS NS NS NS NS NS	Study does not provide evidence that opioid administration among individuals with chronic non-malignant pain has a negative impact on mood or behavior
Vaino et al.(12)	1995	Slow-release oral morphine (50 to 1100 mg/day)*	Cancer patients on morphine Vs. Cancer patients not on morphine	Wartegg personality test Attitude Sense of reality Control Uniformity Opposition Initiative	 NS NS NS NS NS NS	Study does not provide evidence that opioid administration among individuals with chronic non-malignant pain has a negative impact on mood or behavior

NS = no significant adverse drug effect

Stimulants:-Amphetamines and Methylphenidate

A total of six included studies evaluated the effects of Schedule II stimulants on one of the indirect measures of driver crash risk considered in this evidence report (Table 15). Of these six studies, two examined the effects of a stimulant on experimental or simulated driving, five examined the effects of a stimulant on cognitive and/or psychomotor function, and three examined the effects of stimulants on mood or behavior.

All six included studies evaluated the acute effects of stimulants on outcome in stimulant-naïve individuals. Five of the six studies enrolled healthy volunteers; the remaining study, that of Barkley et al.,(5) enrolled adults with ADHD. Our assessment of the effects of stimulants on simulated/experimental driving ability, cognitive and psychomotor function, and mood and behavior is thus limited to their acute effects in healthy individuals and in a small group of adults with ADHD. At the present time one cannot draw any evidence-based conclusions about the effects that the licit long-term use may have on the outcomes of interest in this evidence report.

Table 15. Relevant Outcomes Addressed by Stimulant Studies

Reference	Year	Experimental/Simulated Driving Ability	Motor and/ or Cognitive Performances	Mood or Behavior
Barkley et al.(5)	2005	√	√	
Sliber et al.(7)	2005	√		
Mills et al.(9)	2001		√	√
Clark et al.(15)	1986		√	√
Clark et al.(16)	1986		√	√
Jeffrey et al.(28)	1972		√	
Total number of studies =		2	5	3

Motor and Cognitive Performances: driving related task performed in the laboratory; Mood: Objective and subjective mood scales; Subjective Assessments: Sedation assessed using visual analogue scale (SVAS) or questionnaire and perception of performance

Simulated/Experimental Driving Ability

Two included studies (Overall Quality Score = 8.3; High) assessed the effects of a stimulant on simulated driving.(5,7) The findings of these two studies are presented in Table 16. Neither study provided convincing evidence supporting the hypothesis that stimulants have a deleterious effect on driving ability as measured by performance in a driving simulator.

Table 16. Simulated Driving Ability Following Stimulant Administration

Reference	Year	Opioid (Dose + mode of administration)	Treatment Groups	Driving simulator	Measure of performance	Outcome		Interpretation of Results
Barkley et al.(5)	2005	Methylphenidate 10 mg-oral (single dose) 20 mg-oral(single dose)	Methylphenidate (10 mg) Vs. Methylphenidate (20 mg) Vs. Placebo	FAAC virtual reality driving simulator		10 mg MPH vs. Placebo	20 mg MPH vs. Placebo	No convincing evidence that a single dose of MPH (10 mg or 20 mg) has an impact on driving ability in adults with a clinical diagnosis of ADHD as measured by a simulator.
					Standard Course			
					Simulator self rating	NS	NS	
					Simulator observed rating	NS	NS	
					Average speed (mph)	NS	NS	
					Speed variability (SD)	NS	NS	
					Number of crashes	NS	NS	
					Steering variability	NS	P <0.05	
					Course driving time (secs)	NS	NS	
					Number of turn signals	NS	NS	
					Obstacle Course			
					Average speed (mph)	NS	NS	
					Speed variability (SD)	NS	NS	
					Steering variability	NS	NS	
					Course driving time (secs)	NS	NS	
					Simulator Sickness			
					Self-rating	NS	NS	
					Observer rating	NS	NS	

Reference	Year	Opioid (Dose + mode of administration)	Treatment Groups	Driving simulator	Measure of performance	Outcome	Interpretation of Results
Silber et al.(7)	2005	Dexamphetamine (0.42 mg/kg-single dose)	Dexamphetamine Vs. Placebo	CyberCAR LITE driver training and evaluation simulator	*Simulator Variables (Day: Overall Score)*	P<0.05	Study provides very weak evidence that dexamphetamine has a deleterious impact on daytime (but not nighttime) simulated driving when given as a single dose to healthy individuals.
					Collision	*P* = NS	
					Dangerous action skid	*P* = NS	
					No signal cancel when entering freeway	*P* = NS	
					Incorrect signaling at intersection	*P* = 0.004	
					No signal cancel at intersection	*P* = NS	
					Wheels not straight on approaching intersection	*P* = NS	
					No signal when changing lane	*P* = NS	
					No signal cancel when changing lane	*P* = NS	
					No signal when moving off	*P* = NS	
					No signal cancel when moving off	*P* = NS	
					No signal cancel when overtaking (left)	*P* = NS	
					No signal cancel when overtaking (right)	*P* = NS	
					No signal when overtaking (left)	*P* = NS	
					No signal when overtaking (right)	*P* = NS	
					Inappropriate braking	*P* = NS	
					Driving too fast	*P* = NS	
					No safe following distance	*P* = NS	
					Driving too slow	*P* = NS	
					Straddled barrier line	*P* = NS	
					Wandering	*P* = NS	
					Wide/cut	*P* = NS	
					Released brake inappropriately when stopping	*P* = NS	
					Not sufficient space when stopped	*P* = NS	
					Needless/unnecessary stop	*P* = NS	
					Did not stop at red traffic light	*P* = NS	
					Straddled solid line	*P* = NS	
					Exceeded speed limit	*P* = NS	
					Advanced situation collision	*P* = NS	
					Speed of vehicle when emergency situation occurred (freeway)	*P* = 0.004	
					Speed of vehicle when emergency situation occurred (city)	*P* = NS	
					Reaction time (emergency stop)	*P* = NS	
					Stopping distance from vehicle/object at emergency stop (freeway)	*P* = NS	
					Stopping distance from vehicle/object at emergency stop (freeway)	*P* = NS	
					Skidding when stopping during advanced situation	*P* = NS	
					Simulator Variables (Night: Overall Score)	P = NS	
					Collision	*P* = NS	
					Dangerous action skid	*P* = NS	
					No signal cancel when entering freeway	*P* = NS	
					Incorrect signaling at intersection	*P* = NS	
					No signal cancel at intersection	*P* = NS	

Reference	Year	Opioid (Dose + mode of administration)	Treatment Groups	Driving simulator	Measure of performance	Outcome	Interpretation of Results
					Wheels not straight on approaching intersection	*P* = NS	
					No signal when changing lane	*P* = NS	
					No signal cancel when changing lane	*P* = NS	
					No signal when moving off	*P* = NS	
					No signal cancel when moving off	*P* = NS	
					No signal cancel when overtaking (left)	*P* = NS	
					No signal cancel when overtaking (right)	*P* = NS	
					No signal when overtaking (left)	*P* = NS	
					No signal when overtaking (right)	*P* = NS	
					Inappropriate braking	*P* = NS	
					Driving too fast	*P* = NS	
					No safe following distance	*P* = NS	
					Driving too slow	*P* = NS	
					Straddled barrier line	*P* = NS	
					Wandering	*P* = NS	
					Wide/cut	*P* = NS	
					Released brake inappropriately when stopping	*P* = NS	
					Not sufficient space when stopped	*P* = NS	
					Needless/unnecessary stop	*P* = NS	
					Did not stop at red traffic light	*P* = NS	
					Straddled solid line	*P* = NS	
					Exceeded speed limit	*P* = NS	
					Advanced situation collision	*P* = NS	
					Speed of vehicle when emergency situation occurred (freeway)	*P* = NS	
					Speed of vehicle when emergency situation occurred (city)	*P* = NS	
					Reaction time (emergency stop)	*P* = NS	
					Stopping distance from vehicle/object at emergency stop (freeway)	*P* = NS	
					Stopping distance from vehicle/object at emergency stop (freeway)	No results	
					Skidding when stopping during advanced situation	*P* = NS	

ADHD = Attention deficit and hyperactivity disorder
NS = No significant drug effect
SD = Standard deviation

Cognitive and/or Psychomotor Function

Five included studies (Overall Quality Score = 8.4; High) presented data on the acute effects of stimulants on cognitive and psychomotor function. These five studies used a total of four different instruments to evaluate function with the use of only one instrument being common to more than one study (Table 17). None of these instruments were utilized by three or more studies. Consequently, meta-analysis was not performed (we require data from three or more combinable datasets to be available before we will pool data using meta-analysis) and our assessment of the findings of the five included studies is limited to a qualitative evaluation of the available evidence.

Table 17. Measures of Cognitive and Psychomotor Function Used in Stimulant Studies

Outcomes assessed	Barkley et al.(5) (2005)	Mills et al.(9) (2001)	Clark et al.(15) 1986	Clark et al.(16) (1986)	Jeffrey et al.(28) (1972)	Total number of studies
Visual reaction time					√	1
Continuous performance test (visual)	√					1
Dichotic monitoring (auditory)			√	√		2
Performance online (POL) task (divided attention)		√				1

The results of the five studies are presented in Table 18. None of these studies provide evidence in support of the hypothesis that stimulants have a deleterious effect on cognitive and psychomotor function. If anything, the evidence suggests that stimulants may enhance performance, especially for tasks that require focus and concentration.

Table 18. Cognitive and Psychomotor Function Following Stimulant Administration

Reference	Year	Stimulant (Dose + mode of administration)	Treatment Groups	Measure of performance	Outcome		Interpretation of Results
Barkley et al.(5)	2005	Methylphenidate 10 mg-oral (single dose) 20 mg-oral(single dose)	Methylphenidate (10 mg) Vs. Methylphenidate (20 mg) Vs. Placebo	 <u>*Conner's CPT*</u> Commission errors Omission errors Reaction time Reaction time variability	10 mg MPH vs. Placebo P = NS NS NS NS	20 mg MPH vs. Placebo *P* <0.05* NS NS NS	No evidence that a single dose (10 mg or 20 mg) of MPH has a deleterious effect on cognitive or psychomotor function among healthy individuals. Only significant difference between drug and placebo indicates an improvement in performance following 20 mg MPH.
Mills et al.(9)	2001	Dextroamphetamine 10 mg-oral (single dose)	Dextroamphetamine (10 mg) Vs. Placebo	POL Task (total) Ce D1 D2 D3	 *P* = NS *P* <0.05* *P* <0.05* *P* = NS		No evidence that a single dose (10 mg) of Dextroamphetamine has a deleterious effect on cognitive or psychomotor function among healthy individuals. Significant differences in POL scores suggest that amphetamine enhances reaction time in healthy individuals. Amphetamine appears to cause a "tunneling" effect where performance is improved for items in the central visual system. Performance does not seem to be improved for items in the periphery
Clark et al.(15)	1986	Methylphenidate 0.65 mg/kg-IV	Methylphenidate (65 mg) Vs. Placebo	<u>*Dichotic monitoring (auditory)*</u> *Focused Attention* Target detection rate Error rate Target discrimination Response time *Divided Attention* Target detection rate Error rate Target discrimination Response time	 *P* = NS *P* = NS *P* = NS *P* = NS *P* = NS *P* = 0.012 *P* = NS *P* = NS		No convincing evidence that MPH (65 mg/kg) has a deleterious effect on cognitive or psychomotor function among healthy individuals.

Reference	Year	Stimulant (Dose + mode of administration)	Treatment Groups	Measure of performance	Outcome	Interpretation of Results
Clarke et al.(16)	1986	Methylphenidate 0.65 mg/kg-IV	Methylphenidate (65 mg) Vs. Placebo	<u>*Dichotic monitoring (auditory)*</u> *Focused Attention* Target detection rate Target discrimination Response time *Divided Attention* Target detection rate Target discrimination Response time	 *P* = NS *P* = NS *P* = NS *P* = NS *P* = NS *P* = NS	No evidence that MPH (65 mg/kg) has a deleterious effect on cognitive or psychomotor function among healthy individuals.
Jeffrey et al.(28)	1972	Dextroamphetamine 5 mg-oral (single dose)	Dextroamphetamine (5 mg) Vs. Placebo	Reaction time	*P* <0.01* Effect greater in older individuals	No evidence that a single dose (5 mg) of Dextroamphetamine has a deleterious effect on cognitive or psychomotor function among healthy individuals. Dextroamphetamine improved reaction times in all included individuals with greater improvements being seen in older individuals.

*Drug demonstrates a statistically significant improvement in performance when compared to performance while on placebo

Mood and Behavior

Three included studies (Overall Quality Score = 8.5; High) presented data on the acute effects of a stimulant on mood and/or behavior (Table 19). None of these studies found that stimulants had a deleterious effect on mood or behavior. Rather, the data from the three studies suggest that the effects of the stimulants on mood and behavior were positive. These data should be viewed with caution, however. Mood and behavior data from two of the studies were based on the test subjects self perception. An individual's internal perception of their own behavior while under the influence of a drug cannot be considered as a good indicator of their actual demeanor. Data from the third study are equally suspect because they were based on a rather informal description of the behavior of the test subjects.

Table 19. Mood and Behavior Following Stimulant Administration

Reference	Year	Stimulant (Dose + mode of administration)	Treatment Groups	Measure	Outcome	Interpretation of Results
Mills et al.(9)	2001	Dextroamphetamine 10 mg-oral (single dose)	Dextroamphetamine (10 mg) Vs. Placebo	*Participants perception of sedation and stimulation* Sedative subscale Stimulant subscale *Stanford sleepiness scale*	 *P* = NS *P* <0.05 *P* = NS	No evidence that MPH alters mood or behavior in a manner that might increase risk for a motor vehicle crash
Clark et al.(15)	1986	Methylphenidate 65 mg/kg-IV	Methylphenidate (65 mg) Vs. Placebo	*Subjective mood state*	Individuals on MPH more talkative and commented on feeling that they were more aware and better able to concentrate	No evidence that MPH alters mood or behavior in a manner that might increase risk for a motor vehicle crash
Clark et al.(16)	1986	Methylphenidate 65 mg/kg-IV	Methylphenidate (65 mg) Vs. Placebo	*Subjective mood state* Alertness Increased elation Reduced depression Less lethargic	 *P* = 0.003 *P* = 0.001 *P* = 0.013 *P* = 0.008	No evidence that MPH alters mood or behavior in a manner that might increase risk for a motor vehicle crash

Depressants:-Barbiturates

A total of seven included studies evaluated the effects of Schedule II depressants on one of the indirect measures of driving ability considered in this evidence report (Table 20). Of these studies, one examined the effects of depressants on experimental or simulated driving, six examined the effects of depressants on cognitive and/or psychomotor function, and two examined the effects of depressants on mood or behavior. Note that the most recent study in this evidence base was published in 1984. This is indicative of the fact that unlike opioid and stimulant use, the medical use of barbiturates has diminished over recent years with the advent of more modern drugs with less risk of dependence (none of these are classified as Schedule II drugs).

Table 20. Relevant Outcomes Addressed by Depressant Studies

Reference	Year	Driving performance	Cognitive Motor and/ or Performances	Mood and Behavior
Logsdon et al.(18)	1984		√	
Pishkin et al.(20)	1980		√	
Tansella et al.(22)	1979		√	√
Hindmarch(30)]	1979		√	
Kopriva et al.(25)	1974		√	
Betts et al.(27)	1972	√*		
Malpas et al.(29)	1970		√	√
Total number of studies =		1	6	2

Behavior: Distractibility, difficulty in following direction, impulsivity, inattention, mental slowness, talkative

*Vehicle-Handling Test (parking test, gap estimation, weaving test) (close-course driving?) All subjects used the same vehicle

Simulated/Experimental Driving Ability

One included study (Quality Score = 6.7; Moderate) evaluated the effects of repeated doses (five doses over 36 hours) of a Schedule II depressant (amylobarbitone) on driving ability as measured by a series of low speed vehicle handling tests. Test subjects were all normal healthy individuals. The results of the study provide evidence that therapeutic doses of amylobarbitone, when taken over a period of 36 hours by healthy individuals, will have an impact on driving ability.

Table 21. Driving Ability Following Depressant Administration

Reference	Year	Drug Dose - mode of administration	Treatment Groups	Measure of performance	Outcome	Interpretation of Results
Betts et al.(27)	1972	Amylobarbitone 30 mg - oral (5 doses over 36 hours)	Amylobarbitone (90mg/day) Vs. Placebo	*Vehicle Handling Tests* Weaving test Parking test Gap estimation test	 P = NS P <0.05 P <0.05	Study provides evidence that amylobarbitone has a deleterious effect on low speed vehicle handling.

Cognitive and/or Psychomotor Function

Six included studies (Overall Quality Score = 8.25; High) examined the effects of a depressant on cognitive and/or psychomotor function. The depressant used in all six studies was a barbiturate. Five of these six studies evaluated the acute effects of barbiturates on cognitive and/or psychomotor function in healthy individuals. The sixth enrolled individuals with a diagnosis of anxiety neurosis(22). The six studies used a total of 14 different measurement instruments to evaluate function with the use of only three instruments being common to more than one study (Table 22). None of these instruments were utilized by three or more studies. Consequently, meta-analysis was precluded and our assessment of the findings of the six studies discussed in this section of the evidence report is limited to a qualitative evaluation.

Table 22. Measures of Cognitive and Psychomotor Function Used in Included Studies

Outcomes assessed	Logsdon et al.(18)	Pishkin et al. (20)	Tansella et al.(22)	Hindmarch et al.(30)	Kopriva et al.(25)	Malpas et al.(29)	Total number of studies
Tapping rate			√				1
Choice reaction time (visual)	√			√			2
Reaction time (auditory)			√		√		2
Simple reaction time (visual)		√					1
Simple reaction time (auditory)			√				1
Pursuit Rotor		√					1
Speeded Inference		√					1
Card sorting			√			√	2
Choice Reaction Time				√			1
DSST			√				1
The Symbol coping test			√				1
The Gibson spiral maze			√				1
Cancellation tasks			√				1
Arithmetic			√				1

DSST = Digit Symbol Substitution Test

The results of the six included studies that evaluated the effects of depressants on cognitive and psychomotor function are summarized by

Table 23. Five of the six included studies were single dose studies in which a single dose of a barbiturate was administered and the effects of that drug were observed at a set time point after administration(18,20,25,29,30). The remaining study examined the effects of chronic barbiturate administration among a group of individuals with a clinical diagnosis of anxiety neurosis(22) .

Of the five studies of the acute effects of a barbiturate on cognitive and/or psychomotor function, two evaluated the effects of the drug within an hour or so of administration(18,25). These studies asked the question, "Does barbiturate have a deleterious effect on cognitive and psychomotor function?" The remaining three studies evaluated the effects of the drug the morning after its administration(20,29,30). These latter studies assumed that the link between barbiturate use and a deterioration in cognitive and psychomotor function was established and asked the question, "Do barbiturates still have an impact on cognitive and psychomotor function following a night of sleep?" This latter question is relevant because one of the primary medical indications for a barbiturate is the treatment of insomnia and it is important to know whether functional performance is impaired the next day.

Findings of studies of acute drug administration (immediate outcomes assessment)

Two included studies (Overall Quality Score = 7.0; Moderate) evaluated the effects of the single dose of barbiturate within an hour or so of its administration.(18,25) These studies consistently found that cognitive and psychomotor function was impaired.

Findings of studies of acute drug administration (delayed outcomes assessment)

Three studies (Overall Quality Score = 7.9; Moderate) evaluated the effects of a single dose of barbiturate the morning after its administration(20,29,30). The results of these studies were inconsistent. Hindmarch(30) (Quality Score = 7.9: Moderate) did not find any evidence of reduced cognitive or psychomotor function the morning after administration of a single 100 mg dose of amylobarbitone. Malpas et al.,(29) however, (Quality Score = 8.6; High), found that cognitive and psychomotor function were reduced the morning after administration of a single 100 mg dose of amylobarbitone and a single 200 mg dose of amylobarbitone. Likewise, Pishkin et al.(20) (Quality Score = 4.2; Low) found that a single dose of secobarbital–amobarbital mix (200 mg) had a deleterious effect on complex functional performance the morning after taking the drug. Given the small size of the evidence base and the fact that so many different instruments have been used to evaluate cognitive and psychomotor function, it is not currently possible to determine whether the differences in the findings of the three studies are the consequence of differences in study quality, in enrollees, or in the drugs and doses used. More evidence on the effects of barbiturates on cognitive and psychomotor function the morning after nighttime administration of the drug is required to resolve the current state of ambiguity.

Findings of studies of chronic drug administration

Tansella et al.(22) evaluated the effects of 7 days of amylobarbitone administration in individuals with a clinical diagnosis of anxiety neurosis who had been admitted to a hospital for crisis intervention. The mean dose of amylobarbitone, which was determined individually for each patient, was relatively high (463 mg/day). Of the nine relevant

outcomes measured, only two were significantly impaired. Whether this finding is the consequence of chance, or is representative of a true drug effect is not clear. Until this study has been replicated, it is unclear whether the long-term use of barbiturate in individuals with a psychiatric disorder has an impact on cognitive and/or psychometric function.

Table 23. Cognitive and Psychomotor Function Following Depressant Administration

Reference	Year	Depressant (Dose + mode of administration)	Treatment Groups	Measure of performance	Outcome	Interpretation of Results
Studies of acute drug administration (outcomes assessed within a few hours of administration)						
Logsdon et al.(18)	1984	Secobarbitol 2 mg/kg or 2.9 mg/kg-oral (single dose)	Secobarbital (2 mg/kg or 2.9 mg/kg-oral) Vs. Placebo	*Choice Reaction time (visual)* Visual degradation Character difficulty Rotation Reversal *Choice Reaction time (visual)* Visual degradation Character difficulty Rotation Reversal	 *P* <0.01 *P* <0.01 *P* <0.01 *P* <0.01 *P* <0.01 *P* <0.01 *P* <0.01 *P* <0.01	Study provides evidence that a single dose of secobarbital (>2.0 mg/kg) has a deleterious effect on cognitive and/or psychomotor function.
Kopriva et al.(25)	1974	Pentobarbital Dosage not reported (single dose)	Pentobarbital Vs. No Treatment	*Auditory response time (under monotonous conditions)* Errors of omission Errors of commission	 *P* <0.05 *P* = NS	Study provides evidence that pentobarbital has a deleterious effect on cognitive and/or psychomotor function under monotonous conditions.
Studies of acute drug administration (outcomes assessed the morning after administration)						
Pishkin et al.(20)	1980	Secobarbitol and amobarbital mix 200 mg-oral (single dose)	Barbiturate (200 mg) Vs. Placebo	*Simple reaction time* *Pursuit rotor* *Speeded inference* + +condition 1. - condition Errors (++ condition) Errors (- - condition)	*P* = NS *P* = NS *P* = NS *P* = NS *P* = NS *P* = 0.025	Extremely weak evidence that a single dose of secobarbital/amobarbital mix (200 mg) has a deleterious effect on complex functional performance the morning after taking the drug.
Hindmarch(30)	1979	Amylobarbitone 100 mg-oral (single dose)	Amylobarbitone (100 mg) Vs. Placebo	*Choice Reaction Time*	*P* = NS	No evidence of a deleterious effect on cognitive or psychomotor performance deleterious effect on complex functional performance the morning after taking a single 100 mg dose of amylobarbitone.

Reference	Year	Depressant (Dose + mode of administration)	Treatment Groups	Measure of performance	Outcome	Interpretation of Results
Malpas et al.(29)	1970	Amylobarbitone 100 mg and 200 mg (single dose)	Amylobarbitone (100 mg and 200 mg) Vs. Placebo	*Card Sorting* Motor performance Decision time *Card Sorting* Motor performance Decision time	100 mg *P* = NS *P* <0.05* 200 mg *P* = NS *P* <0.05	Study provides evidence for a deleterious effect in cognitive and/or psychomotor performance the morning after a single 200 mg dose of amylobarbitone.
Studies of chronic drug administration						
Tansella et al.(22)	1979	Amylobarbitone (titrated: mean dose = 463 mg/d for one week	Amylobarbitone (100 mg) vs. Placebo	*Auditory Choice Reaction Task* *Simple Auditory Reaction Time* *Card Sorting* *DSST* *Symbol Coping Test* *Gibson Spiral Maze* *Cancellation Tasks* *Arithmetic* *Tapping rate*	*P* = NS *P* = NS *P* = NS *P* = NS *P* = NS *P* <0.01 *P* = NS *P* = NS *P* <0.01	Results ambiguous. Some evidence that high doses of amylobarbital given for a period of one week have an impact on cognitive or psychomotor function. However, given the number of tests performed this evidence is not convincing.

*Only significant for sorting into 8 categories (2 and 4 categories; *P* = NS)

NS = No evidence of a statistically significant deleterious drug effect

Mood and Behavior

Two included studies (Overall Quality Score = 8.6; High) evaluated the effects of barbiturates on mood and behavior. As noted above, Tansella et al.(22) (Quality Score = 8.6; High) evaluated the effects of 7 days of chronic barbiturate use in individuals hospitalized with anxiety psychosis. These authors found no evidence of an adverse effect of barbiturate on mood or behavior. The only significant drug effect observed was an improvement in the quality of sleep that enrollees experienced. Malpas et al.(29) (Quality Score = 8.6; High) evaluated the effects of two doses of amylobarbitone on mood. Like the findings of Tansella et al., no adverse drug effects were detected and the only drug effect observed was an improvement in quality of sleep.

Table 24. Mood and Behavior Following Depressant Administration

Reference	Year	Depressant (Dose + mode of administration)	Treatment Groups	Measure	Outcome	Interpretation of Results
Tansella et al.(22)	1979	Amylobarbitone (titrated: mean dose = 463 mg/d for one week	Amylobarbitone (100 mg) Vs. Placebo	*Maudsley Personality Inventory* *Manifest Anxiety Scale* *Raven progressive Matrices 38* *Hamilton Anxiety-Rating Scale* *Morbid Anxiety Inventory* *Anxiety Self-Rating* *Insomnia Self-Rating*	*P* = NS *P* = NS *P* = NS *P* = NS *P* = NS *P* = NS *P* <0.01	No evidence that chronic barbiturate use had a negative impact on mood or behavior.
Malpas et al.(29)	1970	Amylobarbitone 100 mg and 200 mg (single dose)	Amylobarbitone (100 mg and 200 mg) Vs. Placebo	*Subjective Mood Scale* *Insomnia Self-Rating*	*P* = NS *P* <0.01	No evidence that chronic barbiturate use had a negative impact on mood or behavior.

NS = No evidence of a statistically significant deleterious drug effect

Section Summary

A number of conclusions can be drawn from the findings of the assessment described above. These conclusions are presented below:

General Conclusion

1. **A paucity of data from studies that enrolled CMV drivers precludes one from directly determining whether the driving ability (as measured using a simulator or on a specific test circuit), cognitive and psychomotor function, or the mood and behavior of CMV drivers is adversely affected by the licit use of any Schedule II opioids.**

   Two included studies enrolled individuals who could potentially be considered to be CMV drivers. Both studies recruited individuals who the study investigators termed, "professional drivers." It is not clear from the articles describing these studies, however, how the study investigators defined a "professional driver." Consequently, it remains a possibility that none, or only a small proportion, of the enrollees in these two studies actually drove large trucks or buses.

Conclusions Related to Licit Opioid Use

1. **A paucity of high-quality data precludes one from drawing an evidence-based conclusion regarding whether first time administration of a Schedule II opioid has a deleterious effect on driving ability.**

   A single small, low-quality study evaluated the effects of a single 50 mg oral dose of codeine on driving ability as measured using a driving simulator in opioid-naïve healthy individuals. This study found that codeine had a significant deleterious effect on driving ability. Because this study is not of high quality, however, and its findings have not yet been replicated, an evidence-based conclusion cannot be drawn at the present time.

2. **A paucity of high-quality data precludes one from drawing an evidence-based conclusion regarding whether licit Schedule II opioid use has a deleterious effect on driving ability among individuals who have used long-term stable doses of the drug for a legitimate medical reason.**

   A single small, low-quality study evaluated the effects of stable doses of various opioids on the driving ability of individuals with chronic pain. No evidence of a driving ability deficit was observed for long-term opioid users on either a community driving course or an obstacle course. Because this study is not of high quality, and its findings have not yet been replicated, an evidence-based conclusion cannot be drawn at the present time.

3. **First time administration of a single therapeutic dose of a Schedule II opioid to opioid-naïve individuals has a deleterious effect on psychomotor and high level (but not low level) cognitive function. (Strength of Evidence: Moderate).**

   Six small, but otherwise high-quality studies assessed the effects of the administration of an opioid on some measures of cognitive (high level) and psychomotor function among opioid-naïve healthy individuals. Four of the six studies found that psychomotor and high-level cognitive function were adversely affected by a single dose of an opioid (morphine, alfentanil, meperidine, or fentanyl). The remaining two studies, both of which evaluated the effects of a single dose of codeine (30 to 100 mg), found no such drug effect. Whether this inconsistency in the findings of the six studies included in this assessment is a consequence of differences in the drugs themselves, in drug dosage, in measurement timing, in the sensitivity of the psychometric instruments used to evaluate cognitive and psychomotor function, in the size of the included studies, or in the characteristics of the individuals who were enrolled in the studies cannot be determined at this time.

4. **Due to a paucity of consistent data from high-quality trials one is precluded from drawing an evidence-based conclusion pertaining to whether chronic (>7days) use of a Schedule II opioid has a deleterious impact on cognitive or psychomotor function at the present time.**

   Five low-quality studies assessed the effects of the long-term administration of an opioid on cognitive and psychomotor function among individuals with chronic pain.

Three of the five included studies did not observe any detrimental effects of opioids on cognitive or psychomotor function. Two studies, however, provide limited evidence supporting the contention that the long-term use of a Schedule II opioid (transdermal fentanyl) may have a deleterious impact on cognitive and psychomotor function.

The reader should note that none of the studies included in the evidence base considered here were designed as non-inferiority or equivalency studies. That is, they were not designed to test the hypothesis that the administration of therapeutic doses of an opioid does not have a deleterious impact on outcome. Rather, the included studies were designed to test the hypothesis that the administration of an opioid will have a deleterious impact on outcome. Failure to disprove the null hypothesis (not observing a treatment effect) by studies that utilize this design cannot be construed as providing evidence of no drug effect. Evidence from such studies, even when consistently observed by several independent studies, can, at best be considered as being suggestive of no treatment effect.

5. **A lack of data from studies that administered a Schedule II opioid to opioid-naïve individuals precludes one from determining whether first time administration of an opioid has a detrimental effect on mood or behavior.**

   No included studies evaluated the effects of opioids on mood or behavior in opioid-naïve individuals.

6. **Presently available data does not provide evidence to support the contention that stable (no change in dose in previous 7 days) therapeutic doses of a Schedule II opioid (morphine) has a detrimental effect on mood or behavior (Strength of Evidence: Weak).**

   Two small, low-quality studies examined the effects of an opioid on mood and/or behavior among individuals with chronic pain. Neither study provided evidence to support the contention that the long-term use of morphine for a licit purpose has a negative impact on mood or behavior.

   As was the case above, the reader should note that neither included study was designed as a non-inferiority or equivalency study (designed to test the hypothesis that the administration of therapeutic doses of opioid does not have a deleterious impact on outcome). Consequently, the finding of no evidence of a deleterious effect cannot be interpreted as providing evidence of no effect.

Conclusions Related to Licit Stimulant Use

1. **A lack of data from controlled trials precludes one from determining whether the licit long-term use of a Schedule II stimulant for the treatment of a legitimate medical condition has a detrimental effect on driving ability (as measured using a simulator or on a specific test circuit), cognitive and psychomotor function, or the mood and behavior such that the risk for a motor vehicle crash is increased.**

No included studies evaluated the effects of the long-term licit use of a stimulant on any of the outcomes relevant to Key Question 2.

2. **A paucity of consistent data precludes one from drawing an evidence-based conclusion pertaining to whether the administration of therapeutic doses of a Schedule II stimulant to stimulant-naïve individuals has a detrimental impact on driving ability.**

   Two high-quality studies assessed the effects of a Schedule II stimulant (dextroamphetamine or methylphenidate) on simulated driving ability. The findings of these two studies were not consistent. One included study did not observe any deleterious effects on simulated driving ability associated with methylphenidate (10mg or 20 mg) when given to individuals with ADHD. The other study found that a single dose of dexamphetamine (0.42 mg/kg) has a deleterious impact on daytime (but not night time) simulated driving in the stimulant-naïve healthy individual. Whether the differences in the qualitative findings of the two studies is the consequence of differences in the drugs tested, in drug dosage, in measurement timing, in the sensitivity of the driving simulators used to evaluate driving ability, in the size of the included studies, or in the characteristics of the individuals enrolled in the studies, cannot be determined at this time.

3. **The best-available evidence does not support the contention that the administration of a single therapeutic dose of a Schedule II stimulant to a stimulant-naïve individual will have a deleterious impact on cognitive and/or psychomotor function (Strength of Evidence: Weak).**

   Five moderate- to high-quality studies presented data on the acute effects of stimulants on cognitive and/or psychomotor function. None of these studies found that the administration of a therapeutic dose of a Schedule II stimulant had a deleterious impact on cognitive or psychomotor function.

   Despite the fact that the overall quality of the evidence base underpinning this conclusion was high and the data from all five studies are qualitatively consistent and robust, we refrain from assigning a "Strength of Evidence" rating of "Strong" to this conclusion. This is because none of the included studies were non-inferiority or equivalency studies (see the previous discussion above, in Conclusion 4 of the opioids section).

4. **The best-available evidence does not support the contention that the administration of a single therapeutic dose of a Schedule II stimulant to a stimulant-naïve individual will have a deleterious impact on domains of mood and/or behavior that are likely to increase the risk for a motor vehicle crash (Strength of Evidence: Weak).**

   Three high-quality studies presented data on the effects of a single dose of a stimulant on mood and/or behavior. None of the studies found that stimulants had a deleterious effect on mood or behavior. In fact data from the three studies suggests that the some of the effects of the stimulants on mood and behavior were positive (improved focus, etc).

Despite the fact that the studies from which these data originated were of high quality, the findings should be viewed with caution. This is because mood and behavior data from two of the three included studies were based on test subject self perception. An individual's internal perception of their own behavior while under the influence of a drug cannot be considered as a good indicator of their actual demeanor. Data from the third study is equally suspect because it was based on a rather informal description of the behavior of the test subjects. To reflect our concern about the potential mischaracterizations of the true mood and behavior states of the individuals enrolled in the included studies, we have downgraded the "Strength of Evidence" rating from High to Weak.

Conclusions Related to Licit Depressant Use

1. **A lack of data precludes one from determining whether the licit long-term use of a Schedule II depressant for the treatment of a legitimate medical condition has a detrimental effect on driving ability (as measured using a simulator or on a specific test circuit), cognitive and psychomotor function, or the mood and behavior such that the risk for a motor vehicle crash is increased.**

   No included studies evaluated the effects of the long-term licit use of a Schedule II depressant on any of the outcomes relevant to Key Question 2.

2. **A paucity of data precludes one from drawing an evidence-based conclusion pertaining to whether the administration of therapeutic doses of a Schedule II depressant to a depressant-naïve individual has a detrimental impact on driving ability.**

   One included moderate-quality study evaluated the effects of repeated doses (five doses over 36 hours) of a Schedule II depressant (amylobarbitone) on driving ability as measured by a series of low speed vehicle handling tests. Test subjects were all normal, healthy individuals. The results of the study suggest that a therapeutic dose of amylobarbitone, when taken over the preceding 36-hour period by healthy individuals, has a detrimental impact on driving ability. Because this study is not of high quality, however, and its findings have not been replicated, an evidence-based conclusion cannot be drawn at the present time.

3. **Therapeutic doses of a Schedule II depressant (secobarbital or pentobarbital) appear to have a deleterious impact on cognitive and psychomotor function (Strength of Evidence: weak).**

   Two moderate-quality studies consistently found that cognitive and psychomotor function was impaired following the administration of a single dose of a Schedule II depressant (secobarbital and pentobarbital). Whether the results of these two studies can be generalized to other depressants in the same class (barbiturates) cannot be determined.

4. **A paucity of consistent data from high-quality trials precludes one from drawing an evidence-based conclusion about whether the deleterious effects of**

Schedule II depressants continue to affect performance the morning after administration of a therapeutic dose.

Because one of the primary medical indications for a Schedule II depressant is insomnia it is important to determine whether the adverse effects that the drugs have on cognitive and psychomotor function can be observed the morning after administration of the drug.

Three studies evaluated the effects of a single dose of barbiturate the morning after its administration. The results of these studies were not consistent with one another. One moderate-quality study did not find any reduction in cognitive and/or psychomotor function the morning after administration of a single 100 mg dose of amylobarbitone. However, the remaining two studies (one administered a single 200 mg dose of amylobarbitone and the other administered a single 200 mg dose of secobarbital/amobarbital mix) found that cognitive and/or psychomotor function were impaired the day after administration of the drug. Whether this inconsistency in the findings of the three included studies is a consequence of between studies differences in the drug dosage, in the sensitivity of the psychometric instruments used to evaluate cognitive and/or psychomotor function, in the size of the included studies, or in the characteristics of the individuals enrolled in the studies cannot be determined at this time.

5. **A paucity of data precludes one from drawing an evidence-based conclusion as to whether the chronic administration of therapeutic doses of a Schedule II depressant has a detrimental impact on cognitive and/or psychomotor function.**

   A single high-quality study evaluated the effects of 7 days of Schedule II depressant (amylobarbitone) administration on cognitive and/or psychomotor function. This study enrolled individuals with a clinical diagnosis of anxiety neurosis who had been admitted to a hospital for crisis intervention. The study found that chronic therapeutic doses of amylobarbitone (463 mg/day) had a deleterious effect on cognitive and psychomotor function. Of the nine relevant outcomes measured, two were significantly impaired. Whether these findings are the consequence of chance, or are representative of a true drug effect is not clear. Replication studies performed with different patient populations and Schedule II depressants are required before evidence-based conclusions about the effects of long-term Schedule II depressant treatment can be drawn.

6. **The best-available evidence currently available does not provide evidence to support the contention that administration of therapeutic doses of a Schedule II depressant (amylobarbitone) has a deleterious impact on mood and/or behavior that might be considered detrimental to motor vehicle safety when administered to depressant-naïve individuals (Strength of Evidence: Weak).**

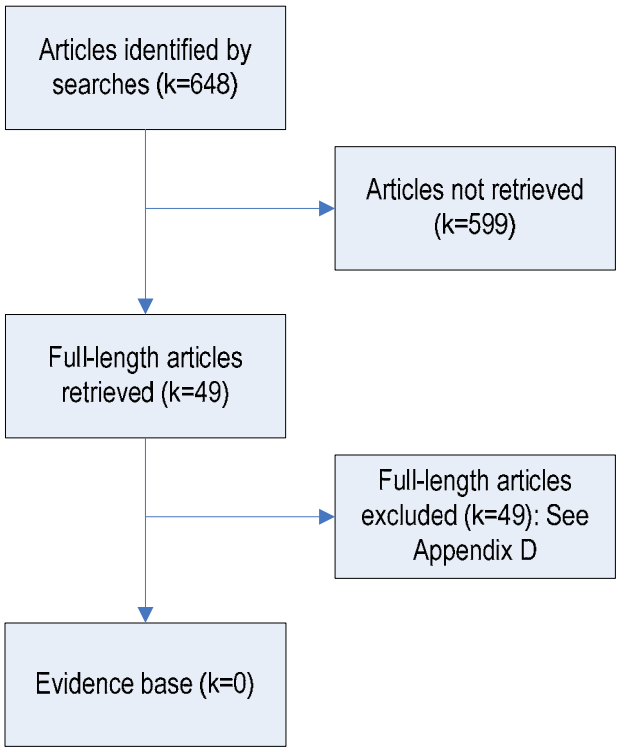
   Two high-quality studies evaluated the effects of acute administration of a Schedule II depressant (amylobarbitone) on the mood and/or behavior of healthy, depressant-naïve individuals. Whether the results of these two studies can be generalized to other depressants in the same class (barbiturates) cannot be determined.

Key Question 3: What is the correlation between the serum level of a Schedule II drug and the risk for a motor vehicle crash?

Identification of Evidence Base

The process by which the evidence base for Key Question 3 was identified is summarized in Figure 6. Our searches[10] identified a total of 648 articles that appeared relevant to this key question. Of these, we retrieved 49 full-length articles. On reading each of the 49 retrieved articles in full, we found that none of them met the inclusion criteria for this key question. Table D-3 of Appendix D lists these 49 articles and provides the reason for each study's exclusion.

Figure 6. Development of Evidence Base for Key Question 3



Section Summary

No conclusions from direct evidence concerning the relationship between the serum level of a Schedule II drug and motor vehicle (any category) crash risk can be drawn at the present time.

Although we identified and retrieved 49 articles that described 49 unique studies, each of which directly examined the relationship between drug use and motor vehicle crash risk, none met the inclusion criteria for this key question

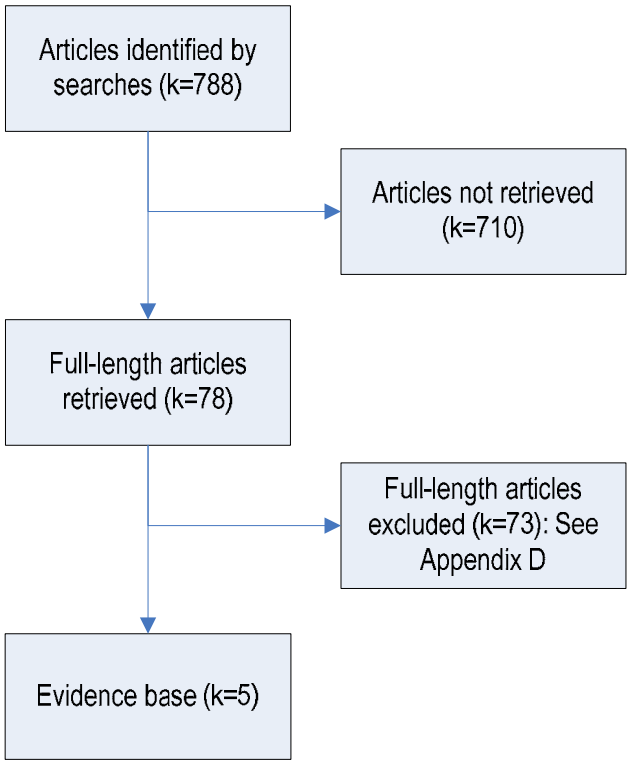
[10] See Appendix A for search strategies

Key Question 4: What is the correlation between the serum level of a Schedule II drug and indirect measures of driving ability?

Identification of Evidence Base

The identification of the evidence base for Key Question 4 is summarized in Figure 7. Our searches[11] identified a total of 788 articles that appeared relevant to this key question. Following application of the retrieval criteria[12] for this question, 78 full-length articles were retrieved and read in full. Of these 78 retrieved articles, five articles were found to meet the inclusion criteria[13] for Key Question 4. Table D-4 of Appendix D lists the 73 articles that were retrieved but then excluded. Table 25 lists the five articles meeting the inclusion criteria for Key Question 4. Complete descriptions of the five studies that comprise the evidence base for this key question are presented in the Study *Summary Tables* of Appendix G.

Figure 7. Development of Evidence Base for Key Question 4



[11] See Appendix A for search strategies
[12] See Appendix B for retrieval criteria
[13] See Appendix C for inclusion criteria

Table 25. Evidence Base for Key Question 4

Reference	Year	Study Location	Country
Sabatowski et al.(8)	2003	Cologne	Germany
Vaino et al.(12)	1995	Helsinki	Finland
Coda et al.(13)	1994	Washington	USA
Westerling et al.(31)	1993	Lund	Sweden
Kerr et al.(14)	1991	Washington	USA

Evidence Base

This subsection provides a brief description of the key attributes of the five studies that comprise the evidence base for Key Question 4. Here we discuss applicable information pertaining to the quality of the included studies and the generalizability of each study's findings to drivers of CMVs. The key attributes of each included study are presented in Table 26.

All five included studies that examined the relationships between the serum level of a drug and the outcomes of interest were studies of opioids (morphine and fentanyl). Of these, three studied the relationship in healthy individuals following a single dose of the drug (13,14,31) and two examined the relationship in chronic opioid users who were being treated for chronic pain(8,12) . All of the studies were small with the largest study enrolling a total of 30 individuals.

Table 26. Key Study Design Characteristics of Studies that Address Key Question 4

Reference	Year	Research question	Drug examined	Study Design	Comparison	Outcomes assessed
Studies of long-term opioid use						
Sabatowski et al.(8)	2003	To evaluate the effects of long-term opioid treatment on psychomotor and cognitive performance measures	Transdermal fentanyl Median dose: 1.35 ng/ml; Range: 0.53-17.7)	Non-randomized controlled trial-Open label	30 chronic non-cancer pain patients on stable doses of fentanyl compared to 90 opioid-free matched healthy controls	1. Test designed to evaluate driving ability in Germany: Sum of the scores of DT, COG and TAVT tests; 2. Motor coordination (2 hand) and VIG
Vaino et al(12)	1995	Do cancer patients receiving long-term morphine analgesia show psychomotor impairment vs. patients not on opioids?	Morphine Sustained-release (oral) Mean dose: 209 mg/day	Non-randomized controlled trial-Open label	24 cancer patients with pain taking long-term sustained-release oral morphine compared to 25 pain-free cancer patients not taking opioids	1. Computerized test battery designed for professional drivers and industrial operators: (5 psychomotor tests) M30,Q1,LL5, Set 3 and peripheral vision test) 2. Wartegg personality test 3. Neural function tests (body sway(eyes open and closed); finger tapping speeds; simple reaction time for auditory, visual, and associative stimuli; Thermal discrimination (warm and cold)
Single dose studies						
Coda et al(13)	1994	To assess the magnitudes of cognitive and motor effects of morphine and alfentanil at different steady plasma opioid concentration and examine the relationship between the magnitude of cognitive and motor effects and plasma concentration of the 2 drugs	Morphine and alfentanil (IV) Plasma concentrations for morphine: 20, 40, and 80ng/ml Plasma concentrations for alfentanil: 16,32 and 64 ng/ml	RCT (Double blind, placebo controlled with crossover)	15 healthy male volunteers received each of the following treatments: morphine, alfentanil and saline (placebo) Minimum of 7 days washout period	1. Motor performance: FTT and isometric force 2. Cognitive performance: RSVP 3. Subjective side effects 4. EEG and sedation
Westerling et al.(31)	1993	To investigate the plasma concentration profile and absolute bioavailability of CR-morphine, and explore the possible relationship between plasma concentration and drug effects	Opioids: Morphine IV infusion of 10 mg morphine HCL; oral solution of 20 mg morphine HCL or controlled release (CR) tablet of 30 mg morphine sulfate.	RCT (Qpen label, with crossover)	10 subjects received three treatments in a randomized order. IV infusion of morphine HCL; oral solution of morphine HCL or controlled release (CR) tablet of morphine sulfate. (at least 1 week washout between treatments)	1. Continuous reaction time (CRT) auditory
Kerr et al.(14)	1991	To evaluate the sensitivity of each cognitive and motor function measure to morphine and examine the relationship between the magnitude of cognitive and motor effects and plasma concentration of morphine	Morphine (IV) Plasma concentrations: 20, 40, and 80 ng/ml	RCT (Double blind, placebo controlled, with crossover)	15 healthy male volunteers received morphine and saline (placebo) Minimum of 7 days washout period	1. Motor performance: FTT and isometric force 2. Cognitive performance: RSVP 3. Memory test and visual perception.

Quality of Evidence Base

The results of our assessment of the quality of the studies included in the evidence base for Key Question 4 are presented in Table 27.

Table 27. Quality of the Studies that Assess Key Question 4

Reference	Year	Quality Scale Used	Quality Score	Quality
Studies of long-term opioid use				
Sabatowski et al.(8)	2003	ECRI Quality Scale I-Comparative Trial	4.2	Low
Vaino et al.(12)	1995	ECRI Quality Scale I-Comparative Trial	4.8	Low
Single-dose studies				
Coda et al.(13)	1994	ECRI Quality Scale II-Comparative Trials (with crossover)	8.4	High
Westerling et al.(31)	1993	ECRI Quality Scale II-Comparative Trials (with crossover)	6.3	Moderate
Kerr et al.(14)	1991	ECRI Quality Scale II-Comparative Trials (with crossover)	8.0	High

Degree to Which Evidence Can e Generalized to Target Population

Important characteristics of the individuals included in the studies that form the evidence base for Key Question 4 are presented in Table 27. None of the included studies enrolled CMV drivers and the generalizability of the correlational data obtained from the five included studies to the target population is unclear. The individuals enrolled in the single dose studies tended to be young, healthy male individuals. Consequently, data from these studies may be generalizable only to a subset of CMV drivers; those aged 20 to 40 who are in very good health.

Individuals enrolled in the two trials that assessed the relationship between serum opioid levels and outcome are fairly representative of the type of individuals who are most likely to require opioids in terms of age. Females, however, are overrepresented in both of these studies. The most likely medical reason for a CMV driver to require opioids is for the treatment of chronic non-malignant pain. However, all of the enrollees in the study of Vaino et al. were suffering from cancer pain. It is unlikely that such individuals would be driving large trucks across country so the relevance of the findings of this study to CMV drivers is unclear.

Table 28. Individuals Enrolled in Studies that Address Key Question 4

Reference	Year	Treatment Group	Age distribution	Disease state	Pain level	Length of education	%Male	%White	Driving experience	Generalizability to CMV drivers
Studies of long-term opioid use										
Sabatowski et al.(8)	2003	n = 30 (Opioid)	Mean 50.0 (SD: 9) years	Chronic pain	Mea n: 3	NR	60	NR	10,000 (Rng: 500-	Fair r

Reference	Year	Treatment Group	Age distribution	Disease state	Pain level	Length of education	%Male	%White	Driving experience	Generalizability to CMV drivers
			(Rng: 34-65)		(Rng: 0-8) VAS				60,000)	
		n = 90 (Controls)	Mean: 50.0 (SD: 9) years (Rng: 34-65)	Healthy	No pain	NR	63	NR	NR	
Vaino et al.(12)	1995	n = 24 (Opioid)	Mean: 53.0 (SD: 9.4) years	Cancer	NR	Mean: 11 years (Basic education)	50	NR	NR	Unclear
		n = 25 (Controls)	Mean: 51.0 (SD: 11.2) years	Cancer	NR	Mean: 12 years (Basic education)	40	NR	NR	
Single-dose studies										
Coda et al.(13)	1994	n = 15 (Crossover -opioid and placebo)	Rng: 21–37 years	Healthy	No pain	NR	100	NR	NR	Unclear
Westerling et al.(31)	1993	n = 10 (Crossover opioid IV, oral solution or CR tablet	Range: 25 to 56 years	Healthy	No pain	NR	60	NR	NR	Unclear
Kerr et al.(14)	1991	n = 15 (Crossover - opioid and placebo)	Rng: 21–37 years	Healthy	No pain	NR	100	NR	NR	Unclear

Findings

Details of which of the outcomes of interest were addressed by the five included studies are presented in Table 29. None of the studies examined the relationship between serum levels of opioid and driving ability or mood and behavior. All five studies examined the relationship between serum opioid level and various measures of cognitive or psychomotor function.

Table 29. Outcomes Assessed by Studies Addressing Key Question 4

Reference	Year	Experimental/Simulated Driving	Motor and/ or Cognitive Performances	Mood* or Behavior†
Studies of long-term opioid use				
Sabatowski et al.(8)	2003		√	
Vaino et al.(12)	1995		√	
Single-dose studies				
Coda et al.(13)	1993		√	
Westerling et al.(31)	1993		√	

Reference	Year	Experimental/Simulated Driving	Motor and/ or Cognitive Performances	Mood* or Behavior†
Kerr et al.(14)	1991		√	
Total number of studies =		0	5	0

Cognitive and/or Psychomotor Function

All five included studies evaluated the relationship between serum opioid levels and cognitive or psychomotor function. These five studies utilized a total of 19 different psychometric tests (Table 30). As was the case above (see Key Question 2), there was very little overlap in the instruments that were used by the different studies. Only the FTT was used in more than two studies (the minimum number of studies required for a meta-analysis). Performing a meta-analysis of data from this instrument alone cannot be justified because it represents only a small proportion of the total quantity of available evidence. Consequently, our assessment of the findings of the five studies that address Key Question 4 is limited to a qualitative assessment of the available evidence.

Table 30. Measures of Cognitive and Psychomotor Function Used in Correlational Studies

Outcome assessed	Sabatowski et al.(8) (2003)	Vaino et al.(12) (1995)	Coda et al.(13) (1993)	Weterling et al.(31) 1993	Kerr et al.(14) (1991)	Total number of studies
FTT		√	√		√	3
Isometric force			√		√	2
Simple reaction time (Visual)		√				1
Simple reaction time (Auditory)		√				1
Simple reaction time (Associative)		√				1
Continuous reaction time (Auditory)				√		1
DT	√					1
Coordination (2-hand)	√					1
COG	√					1
VIG	√					1
TAVT	√					1
Visual perception					√	1
RSVP			√		√	2
Memory test (NS)					√	1
M30		√				1
Q1		√				1

Outcome assessed	Sabatowski et al.(8) (2003)	Vaino et al.(12) (1995)	Coda et al.(13) (1993)	Weterling et al.(31) 1993	Kerr et al.(14) (1991)	Total number of studies
LL5		√				1
SET 3		√				1
Peripheral vision test		√				1

COG = (Attention test); DT = Determination test; FTT = Finger Tapping Test; NS = Not specified; RSVP = Rapid Single Visual Presentation; TAVT = Test for visual orientation, tachistoscopic perception; VIG = Vigilance test; Computerized test battery designed for professional drivers and industrial operators (psychomotor tests): M30, Q1, LL5, Set3.

The findings of the five studies that looked for relationships between serum levels of opioids and measures of cognitive and/or psychometric function are presented in Table 31.

Relationships between Serum Opioid Levels and Measures of Cognitive and Psychomotor Function in Opioid-Naïve Individuals

All three included studies (Overall Quality Score = 8.0: High) demonstrated the existence of a relationship between serum levels of opioid and some (but not all) measures of cognitive and/or psychomotor dysfunction. The measures that demonstrated the strongest relationship tended to be measures of higher order functioning. The degree of between patient variance increased as serum opioid concentration increased. This is reflective of the fact that the effect of the same concentration of opioid will have a different impact on different individuals. Thus, some individuals will demonstrate cognitive or psychomotor function when serum opioid levels are high, others will not.

Relationships between Serum Opioid Levels and Measures of Cognitive and Psychomotor Function in Licit Long-Term Opioid Users

Both included studies (Overall Quality Score = 4.6: Low) identified relationships between serum levels of opioid and a number of measures of cognitive and/or psychomotor function. Despite this relationship, none of the outcome measures were statistically significantly different from normal (See Findings for Key Question 2).

Table 31. Relationship between Schedule II Drug Serum Level and Cognitive and/Psychomotor Function

Reference	Year	Drug examined	Findings	Conclusions
Studies of long-term opioid use				
Sabatowski et al.(8)	2003	Transdermal fentanyl [median plasma concentration: 1.35 ng / m; range 0.53 – 17.7]	Statistically significant correlation between plasma fentanyl levels and the following items: Number of errors (r = 0.673; P = 0.002), mean reaction time (r = 0.48; P = 0.04) Score of the vigilance testing of PP-group (r = 0.573; P = 0.01)	Significant relationship between serum levels of fentanyl and mean reaction time and vigilance test observed.
Vaino et al.(12)	1995	Sustained- release oral morphine [mean plasma concentration: 66 ng / ml; SD 79; range 4.5-337)	Statistically significant correlation between plasma morphine and the following: Q1 test (r = 0.74; P <0.005) LL5 errors (r = 0.85; P <0.005) Statistically significant correlation between plasma morphine3-glucuronide: Q1 test (r = 0.61; P <0.05) LL5 errors (r = 0.93; P <0.001)	Significant relationship between serum levels of morphine and the performance of tasks demanding special concentration observed.
Single-dose studies				
Coda et al.(13)	1994	Morphine and alfentanil continuous infusion (IV) Morphine plasma concentrations: 20, 40, 80 ng/ ml ; Alfentanil plasma concentrations: 16, 32, 64 ng /ml)	RSVP: Reading time significantly increased at the highest alfentanil and morphine target concentration (P <0.05) Isometric force: Significant decrease in accuracy of force maintenance at the high target levels of morphine and alfentanil ; error was greater when subject could not rely on vision (P <0.05) Tapping: Morphine and alfentanil did not affect tapping	Continuous infusion of morphine and alfentanil impair some key elements of cognition and motor function within the range of plasma opioid concentrations associated with clinical analgesia. The magnitude of effects on sensitive elements of cognition and motor function are related to plasma concentration.
Westerling et al.(31)	1993	Opioids: Morphine IV infusion of 10 mg morphine HCL; oral solution of 20 mg morphine HCL or controlled release (CR) tablet of 30 mg morphine sulfate.	A significant slight prolongation of mean Continuous Reaction Time observed as was a markedly increased variability in reaction times at the higher plasma morphine concentration obtained after I.V. infusion	Increased variations of CRTs were related to plasma concentration of morphine and found to be more pronounced at the higher plasma concentration obtained after I.V. infusion.
Kerr et al.(14)	1991	Morphine continuous infusion (IV) (plasma concentrations: 20, 40, 80 ng/ ml)	RSVP: Reading time significantly increased at the medium and high target levels of MS and deficits increase with plasma concentration(P <0.01) (subjects slowed considerably in their ability to encode and process verbal information) - Delayed memory significantly impaired with all MS levels(P <0.01) Isometric force: Ability to maintain low consistent levels of force significantly decreased at the high target MS concentration, with greater deficit when subject could not rely on vision (with vision and without vision absolute error was greater for morphine than saline, P <0.05 and P <0.001, respectively) Tapping: Small (0.3 taps per second) decrement in preferred hand tapping at the highest target concentration of morphine.(P <0.05)	Strong effects of morphine on some (but not all) cognitive measures and motor function tasks; the degree of impact was related to plasma concentration of morphine.

Section Summary

A number of conclusions can be drawn from the findings of the analyses described above. These are presented below:

1. **A lack of evidence precludes one from drawing evidence-based conclusions about the relationship between serum levels of Schedule II stimulants and depressants and any of the outcomes of interest (driving ability, cognitive and/or psychomotor function, and mood and behavior).**

   No study meeting the inclusion criteria for Key Question 4 evaluated a Schedule II stimulant or depressant.

2. **A lack of evidence precludes one from drawing evidence-based conclusions about the relationship between serum levels of Schedule II opioids and driving ability or mood and behavior.**

   No study meeting the inclusion criteria for Key Question 4 investigated the relationship between the serum level of a Schedule II opioid and driving ability or mood and behavior.

3. **The magnitude of the acute cognitive and psychomotor functional deficits observed among opioid-naïve individuals following administration of a single dose of Schedule II opioid are correlated with the serum level of the drug (Strength of Evidence: Strong).**

   Three moderate to high-quality studies observed a relationship between serum levels of a Schedule II opioid (morphine) and some (but not all) measures of cognitive and/or psychomotor dysfunction. The measures that demonstrated the strongest relationship with drug serum level tended to be measures of higher order functioning.

4. **Measures of high level cognitive and psychomotor function are inversely correlated with the serum level of Schedule II opioids (Strength of Evidence: Weak).**

   Two low-quality studies observed significant correlations between serum levels of Schedule II opioids (fentanyl and morphine) and a number of high level measures of cognitive and/or psychomotor function.

Key Question 5: Is there a relationship between the pharmacokinetics of a Schedule II drug and the risk for a motor vehicle crash?

In addition to examining the effects of specific Schedule II drugs on driver safety and attempting to describe the relationship between serum level and crash risk, consideration must also be given to the pharmacokinetics (the absorption, distribution, metabolism, and elimination of drugs) of these drugs. Because of the normal aging process, development of illnesses, and the concurrent use of other drugs, one would expect that the pharmacokinetics of any drug will differ considerably across individuals (and even within

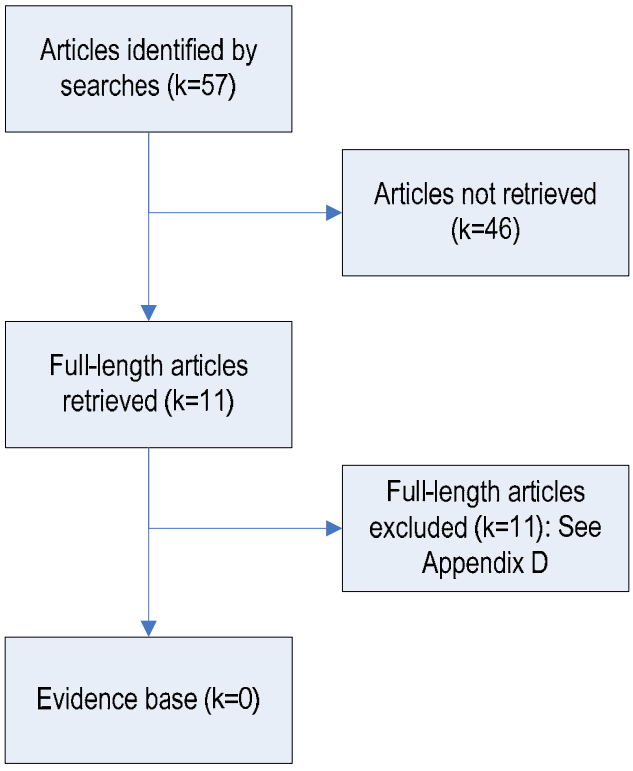
an individual over time). It is thus possible that the driver safety profile associated with a specific Schedule II drug may be different in different individuals even though they are taking the same drug. For example, an individual with kidney disease may not be able to eliminate a drug as quickly as a healthy individual. Consequently, the serum level of the drug may be maintained at higher levels for longer in the former individual. This in turn may alter that individuals risk for a motor vehicle crash.

The purpose of this section of the report is to determine whether the pharmacokinetics of a Schedule II drug have an impact on motor vehicle crash risk and, if so, to identify the specific factors that influence this risk.

Identification of Evidence Base

The identification of the evidence base for Key Question 5 is summarized in Figure 8. Our searches[14] identified a total of 57 articles that appeared relevant to this key question. Following application of the retrieval criteria[15] for this question, 11 full-length articles were retrieved and read in full. None of these articles were found to meet the inclusion criteria16 for Key Question 5. **Table D-5** of Appendix D lists the 11 articles that were retrieved but then excluded and provides a reason for their exclusion.

Figure 8. Development of Evidence Base for Key Question 5



[14] See Appendix A for search strategies
[15] See Appendix B for retrieval criteria
[16] See Appendix C for inclusion criteria

Section Summary

No conclusions can be drawn from direct evidence on the relationship between Schedule II drug pharmacokinetics and motor vehicle (any category) crash risk at the current time.

Although we identified and retrieved 11 articles that described 11 unique studies, each of which directly examined the relationship between drug use and motor vehicle crash risk, none provided data on the relationship between crash risk and the pharmacokinetics of a Schedule II drug.

Key Question 6: Is there a relationship between the pharmacokinetics of a Schedule II drug and indirect measures of driving ability?

In a previous section of this evidence report (*Key Question 4*) we noted that available evidence suggests that a relationship between serum drug levels and cognitive and psychomotor performance exists in both healthy, opioid-naïve individuals and chronic opioid users. In this section of the evidence report, we investigate how the pharmacokinetics of Schedule II drugs impact indirect measures of driving ability, and attempt to identify the specific factors that influence this relationship. In particular, we look for data describing the relationship between Schedule II drug concentrations and the magnitude of functional and emotional impairment as a function of time following dosing. Attaining an understanding of the temporal relationships between drug concentration and performance for different Schedule II drugs is important because it will allow one to provide guidance on when after dosing one might be most likely to see performance deficits if they are going to occur.

Identification of Evidence Base

The identification of the evidence base for Key Question 6 is summarized in Figure 9. Our searches[17] identified a total of 103 articles that appeared relevant to this key question. Following application of the retrieval criteria[18] for this question, 15 full-length articles were retrieved and read in full. Of these 15 retrieved articles, four articles were found to meet the inclusion criteria[19] for Key Question 6. Table D-6 of Appendix D lists the 11 articles that were retrieved but then excluded and provides a reason for their exclusion. Table 32 lists the four articles meeting the inclusion criteria for Key Question 6. Complete descriptions of the studies include in the evidence base for this question are presented in *Study Summary Tables* that comprise Appendix G.

[17] See Appendix A for search strategies
[18] See Appendix B for retrieval criteria
[19] See Appendix C for inclusion criteria

Figure 9. Development of Evidence Base for Key Question 6

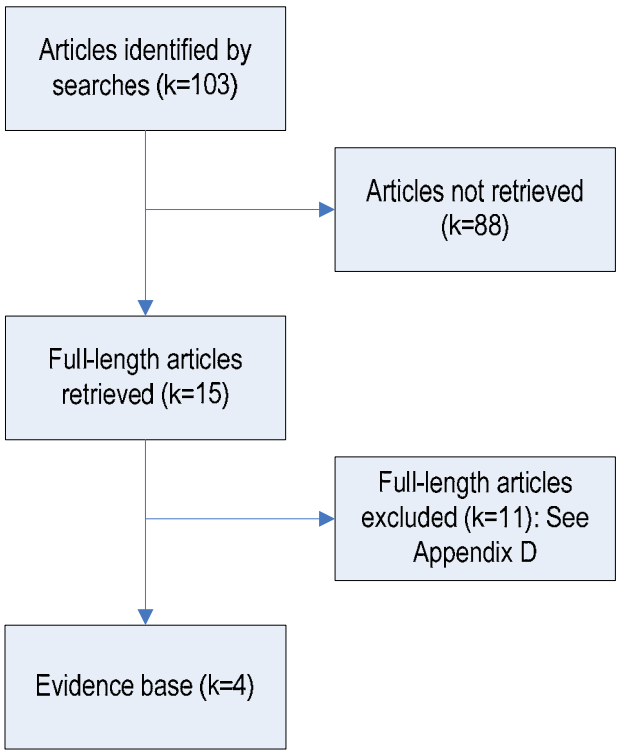


Table 32. Evidence Base for Key Question 6

Reference	Year	Study Location	Country
Mills et al.(9)	2001	North Carolina	USA
Westerling et al.(31)	1993	Lund	Sweden
Ghoneim et al.(23)	1975	Iowa	USA
Kortilla et al.(24)	1975	Helsinki	Finland

Evidence Base

This subsection provides a brief description of the key attributes of the four studies that comprise the evidence base for Key Question 6. Here we discuss applicable information pertaining to the quality of the included studies and the generalizability of each study's findings to drivers of CMVs. The key attributes of each included study are presented in Table 33.

Three of the four included studies evaluated the relationship between the pharmacokinetics of an opioid (morphine, fentanyl, or meperidine) and one of the outcomes of interest. The fourth included study investigated the relationship between a stimulant (dextroamphetamine) and outcome. All four included studies investigated the relationship between the pharmacokinetics of a Schedule II drug in healthy volunteers who were naïve to the drugs used. Relevant data obtained from chronic licit Schedule II drug users is not available at the present time.

Table 33. Key Study Design Characteristics of Studies that Address Key Question 6

Reference	Year	Research question	Drug examined	Study Design	Comparison	Outcomes assessed
Opioid Studies						
Westerling et al.(31)	1993	To investigate the plasma concentration profile and absolute bioavailability of morphine controlled release (CR),and explore the possible relationship between plasma concentration and drug effects	Morphine IV infusion of 10 mg morphine HCL; oral solution of 20 mg morphine HCL or controlled release (CR) tablet of 30 mg morphine sulfate.	RCT (Qpen label, crossover, randomized)	10 healthy volunteers received three treatments in a randomized order. IV infusion of morphine HCL; oral solution of morphine HCL or controlled release (CR) tablet of morphine sulfate. (at least 1 week washout between treatments)	1. Continuous reaction time (auditory)
Ghoneim et al.(23)	1975	To what extent does a single dose of fentanyl affect mental and psychomotor functions and how fast is the recovery of these functions?	Fentanyl (IV) 0.1 or 0.2 mg	RCT (Double-blind, placebo controlled with crossover)	Ten healthy male volunteers received each of the following treatments: fentanyl, diazepam and placebo (at weekly interval)	1. Backward digit span 2. Tapping board 3. Serial learning, 4. Short term memory 5. Delayed recall 6. Simple reaction time 7. Choice reaction time 8. Visual retention tests 9. Subjective rating
Kortilla et al.(24)	1975	To examine the effects of Meperidine on psychomotor skills related to driving.	Meperidine 75mg (IM)	RCT (Double-blind, placebo controlled with crossover)	11 healthy volunteers tested before and after IM injection of saline, diazepam or meperidine	1. Psychomotor tests: reaction time, coordination test, CFF 2. Subjective assessments.
Stimulant Studies						
Mills et al.(9)	2001	To examine the influence of stimulants and sedatives on single-target and divided-attention responses in different parts of the visual field	Stimulant: Dextroamphetamine (oral) 10mg	RCT (Double-blind, placebo controlled with crossover)	18 healthy volunteers received each of the following treatments: a single dose of alprazolam, a single dose of dextroamphetamine and a single dose of placebo (three-day washout periods)	1. Performance online or POL task 2. Subjective assessments: perception of sedative or stimulants drug effects and the Stanford Sleepiness Scale

Quality of Evidence Base

The results of our assessment of the quality of the studies included in the evidence base for Key Question 6 are presented in Table 34.

Table 34. Quality of the Studies that Assess Key Question 6

Reference	Year	Quality Scale Used	Quality Score	Quality
Opioid Studies				
Westerling et al.(31)	1993	ECRI Quality Scale II-Comparative Trials (with crossover)	6.3	Moderate
Ghoneim et al.(23)	1975	ECRI Quality Scale II-Comparative Trials (with crossover)	8.8	High
Kortilla et al.(24)	1975	ECRI Quality Scale II-Comparative Trials (with crossover)	8.6	High
Stimulant Studies				
Mills et al.(9)	2001	ECRI Quality Scale II-Comparative Trials (with crossover)	8.5	High

Generalizability of Evidence to Target Population

Important characteristics of the individuals included in the studies that form the evidence base for Key Question 6 are presented in Table 35. None of the included studies enrolled CMV drivers and the generalizability the relationships between drug pharmacokinetics observed by the four included studies to the target population is unclear. As was the case for Key Question 4, the individuals enrolled in the included studies were healthy, young individuals and data from these studies may be generalizable to only a small subset of CMV drivers; those aged 20–40 who are in good health.

Table 35. Individuals Enrolled in Studies that Address Key Question 6

Reference	Year	Treatment Group	Age distribution	Disease state	Pain level	Length of education	%Male	%White	Driving experience	Generalizability to CMV drivers
Opioid Studies										
Westerling et al.(31)	1993	n = 10 (Crossover opioid IV, oral solution or controlled release (CR) tablet	Range: 25 to 56 years	Healthy	NR	NR	60%	NR	NR	Unclear
Ghoneim et al.(23)	1975	n = 10 (Crossover- opioid, diazepam, and placebo)	Mean: 22.9 (SD: 1.5) years	Healthy	No pain	NR	100%	NR	NR	Unclear
Kortilla et al.(24)	1975	n = 11 (Crossover opioid, diazepam or placebo)	Mean: 25 (SD:2.6) years	Healthy	No pain	(Students volunteers)	73%	NR	NR	Unclear
Stimulant Studies										
Mills et al.(9)	2001	n = 18 (crossover stimulant, sedative, and placebo	Mean: 29.9 (Range: 19-37) years	NR	NR	NR	22.8%	77.8%	NR	Unclear

Findings

Details of which of the outcomes of interest were addressed by the four included studies are presented in Table 36. None of the studies examined the relationship between the pharmacokinetics of a Schedule II drug and experimental or simulated driving, or mood and behavior. All four studies examined the relationship between the pharmacokinetics of a Schedule II drug and cognitive and/or psychomotor function.

Table 36. Outcomes Assessed by Studies that Address Key Question 6

Reference	Year	Experimental/Simulated Driving	Motor and/ or Cognitive Performances	Mood* or Behavior†
Opioid Studies				
Westerling et al.(31)	1993		√	
Ghoneim et al.(23)	1975		√	
Kortilla et al.(24)	1975		√	
Stimulant Studies				
Mills et al.(9)	2001		√	
Total number of studies =		0	4	0

Cognitive and/or Psychomotor Function

As stated above, all four included studies (Overall Quality Score: 8.6: High) evaluated the relationship between the pharmacokinetics of a Schedule II drug and cognitive or psychomotor function. These four studies utilized a total of 13 different psychometric tests (Table 37). There was no overlap in the instruments used to measure cognitive and psychomotor function across the studies included in this evidence base. Performing a meta-analysis of data from these studies cannot be justified because each instrument is measuring a slightly different aspect of functioning. Consequently, our assessment of the findings of the five studies that address Key Question 4 is limited to a qualitative assessment of the available evidence.

Table 37. Measures of Cognitive and Psychomotor Function Used by Included Studies

Outcome assessed	Mills et al.(9) 2001	Westerling et al.(31) 1993	Kortilla et al.(24) 1975	Ghoneim et al.(23) 1975	Total number of studies
Continuous reaction time (auditory)		√			1
Choice reaction time (Visual and auditory)			√		1
Choice reaction time (Visual				√	1
Simple reaction time (Visual)				√	1
Coordination test			√		1
CFF			√		1
Backward digit span				√	1
Tapping board				√	1
Serial learning				√	1
Short term memory				√	1
Delayed recall				√	1
Visual retention test				√	1
Performance online or POL task (visual)	√				1

CFF = Critical Flicker-fusion test

The findings of the four studies that addressed Key Question 6 are presented in Table 38.

Table 38. Schedule II Drug Pharmacokinetics and Cognitive and/or Psychomotor Function

Reference	Year	Drug examined	Findings	Conclusions
Opioid Studies				
Westerling et al.(31)	1993	Morphine morphine HCL (IV - 10 mg; morphine HCL (oral 20 mg) or morphine sulfate (CR tablet-30 mg)	Significant prolongation of mean CRT observed as was markedly increased variability in reaction times at the higher plasma morphine concentration obtained after I.V. infusion Plasma concentration produced after intake of the CR tablet lower than after intake of immediate release morphine solution, but maintained at a plateau for at least 12 hours. At 6,12,and 24 h after the CR tablet was given, mean plasma concentrations were 11.3 ±6, 5.6 ±3.3 and 6.1 ±1.3 nmol / L, respectively.	Increased variations of CRTs were related to plasma concentration of morphine and found to be more pronounced at the higher plasma concentration obtained after I.V. infusion
Ghoneim et al.(23)	1975	Fentanyl -0.1 or 0.2 mg- (I.V)	*Tapping board* At 2 hours-effects of the low dose of fentanyl not significantly different from placebo, while the high dose of fentanyl significantly lowered performance. Performance returned to the placebo level at the 6th hour test. *Subjective questionnaire* All treatments resulted in a highly significant sedative effect at the 0.5 hr post-injection test (P <0.01). The high dose of the drug was still effective in producing physical sedation at the 2nd hour post-injection testing (P <0.01), while the low dose no longer produced significant effects. The same was true for mental sedation. By 6 hrs no statistically significant effects were evident.	On the Objective psychological tests, the low dose of fentanyl had no measurable effects at 2 hours post-injection, while the high dose of fentanyl significantly lowered performance. This was clearly demonstrated in the tapping performance. Recovery was complete by the 6th hour according to the psychological tests.
Kortilla et al.(24)	1975	Meperidine 75mg (IM)	Highest concentration of meperidine (179±66 ng / ml) in serum (mean ±SD) was measured 1 hour after injection, after which it declined as function of time. Meperidine impaired reactive time for as long as 3 hours and flicker-fusion discrimination and coordination for as long as 12 hours. All the results at 24 hours were similar to those measured before the injection of meperidine.	The authors concluded that patients should not drive or operate machinery for at least 24 hours after receiving 75 mg meperidine intramuscularly. One should remember that the results of this study were obtained in young healthy subjects; the effects of the drug in older or ill patients could be more harmful and more prolonged.
Stimulant Studies				
Mills et al.(9)	2001	Dextroamphetamine 10mg (oral)	Peak dextroamphetamine concentration occurred between 1.5 and 4hr, with a mean Tmax of 2.78 hr There was an overall significant increase in COMP scores that coincided with rising dextroamphetamine plasma levels and preceded the plasma peak by about 1-1.5 hr (dextroamphetamine vs. placebo. P = 0.0406). Significant increased subjective ratings were observed immediately after the 10 mg dextroamphetamine administration (15 min), reaching a peak at 45 min postdose, then gradually dissipating as the plasma levels peaked over the next 2 hr.	Significant increase in COMP scores and significant increased subjective rating preceded the plasma peak concentration of dextroamphetamine and treatment effects evident or the hours closest to the maximum plasma concentration

CRT = Continuous Reaction Time; COMP = linear combination of all

Section Summary

1. **A lack of evidence precludes one from drawing evidence-based conclusions about the relationship between the pharmacokinetics of Schedule II drugs and driving ability (as measured by a simulator or on a prespecified driving course).**

   No studies of Schedule II drugs meeting the inclusion criteria for Key Question 6 addressed this outcome.

2. **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)**

   Three included studies demonstrated the existence of the relationship between the pharmacokinetics of a Schedule II opioid (morphine, fentanyl, or meperidine) and temporal changes in measures of cognitive and psychomotor function.

3. **A lack of data precludes one from drawing evidence-based conclusions about the relationship between the pharmacokinetics of a Schedule II opioid and temporal changes in measures of cognitive and psychomotor function in chronic licit users of the drugs.**

   No studies of Schedule II drugs meeting the inclusion criteria for Key Question 6 addressed this question in a population of chronic licit users of opioids.

4. **A paucity of evidence precludes one from drawing evidence-based conclusions about the relationship between the pharmacokinetics of Schedule II stimulants and temporal changes in measures of cognitive and psychomotor function in healthy stimulant-naïve individuals.**

   A single included study investigated the relationship between the pharmacokinetics of a Schedule II stimulant (dextroamphetamine) and temporal changes in cognitive and psychomotor function in healthy stimulant-naïve individuals. This small, but otherwise high-quality study demonstrated a temporal relationship between dextroamphetamine concentration and cognitive function. Because of the small size of the study, replication is required before evidence-based conclusions can be drawn.

5. **A lack of data precludes one from drawing evidence-based conclusions about the relationship between the pharmacokinetics of a Schedule II stimulant and temporal changes in measures of cognitive and psychomotor function in chronic licit users of the drugs.**

   No studies of Schedule II drugs meeting the inclusion criteria for Key Question 6 addressed this question in a population of chronic licit users of stimulants.

6. **A lack of evidence precludes one from drawing evidence-based conclusions about the relationship between the pharmacokinetics of Schedule II depressants and temporal changes in measures of cognitive and psychomotor function.**

No studies of Schedule II depressants meeting the inclusion criteria for Key Question 6.

7. **A lack of evidence precludes one from drawing evidence-based conclusions about the relationship between the pharmacokinetics of Schedule II drugs and temporal changes in mood or behavior.**

   No studies of Schedule II drugs meeting the inclusion criteria for Key Question 6 addressed this outcome.

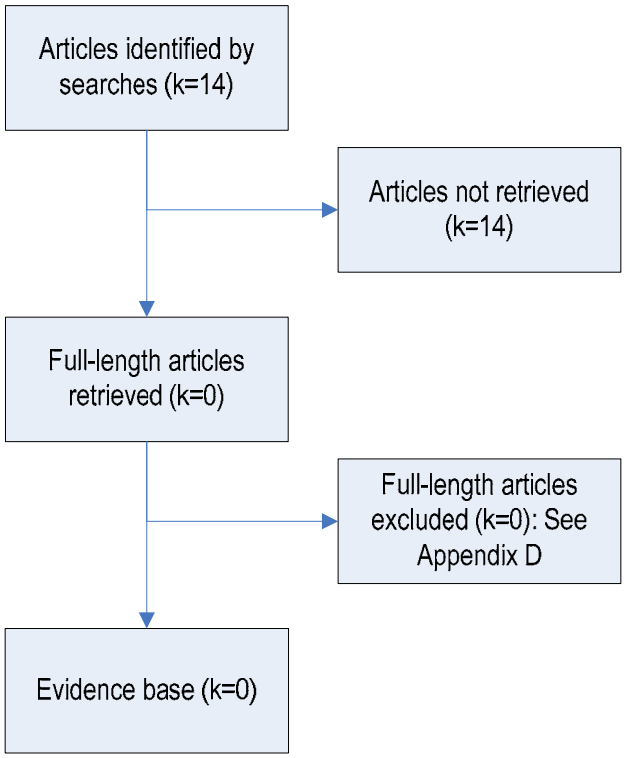
Key Question 7: Are there common drug interactions that include a prescribed Schedule II drug that increase the risk for a motor vehicle crash?

The fact that alcohol will enhance the negative effects on cognitive and psychomotor function of Schedule II drugs is well established. Consequently, we focus on the evaluation of drug interactions with a Schedule II drug other than alcohol.

Identification of Evidence Base

The identification of the evidence base for Key Question 7 is summarized in Figure 10. Our searches[20] identified a total of 14 articles that appeared relevant to this key question. On reviewing the abstracts for these articles, none of them were found to meet the retrieval criteria.

Figure 10. Development of Evidence Base for Key Question 7



[20] See Appendix A for search strategies

Section Summary

No conclusions from direct evidence concerning the interaction between a Schedule II drug with another drug and motor vehicle (any category) crash risk can be drawn at the present time.

Although our searches identified 14 potentially relevant articles, none of them were found to meet the retrieval criteria.

Key Question 8: Are there common drug interactions that include a prescribed Schedule II drug that affect indirect measures of driving ability?

Identification of Evidence Base

The identification of the evidence base for Key Question 8 is summarized in Figure 11. Our searches[21] identified a total of 31 articles that appeared relevant to this key question. Following application of the retrieval criteria[22] for this question, eight full-length articles were retrieved and read in full. Of these eight retrieved articles, four articles were found to meet the inclusion criteria[23] for Key Question 8. Table D-7 of Appendix D lists the four articles that were retrieved but then excluded and provides a reason for their exclusion. Table 39 lists the four articles meeting the inclusion criteria for Key Question 8. Complete descriptions of the studies include in the evidence base for this question are presented in *Study Summary Tables* that comprise Appendix G.

[21] See Appendix A for search strategies
[22] See Appendix B for retrieval criteria
[23] See Appendix C for inclusion criteria

Figure 11. Development of Evidence Base for Key Question 8

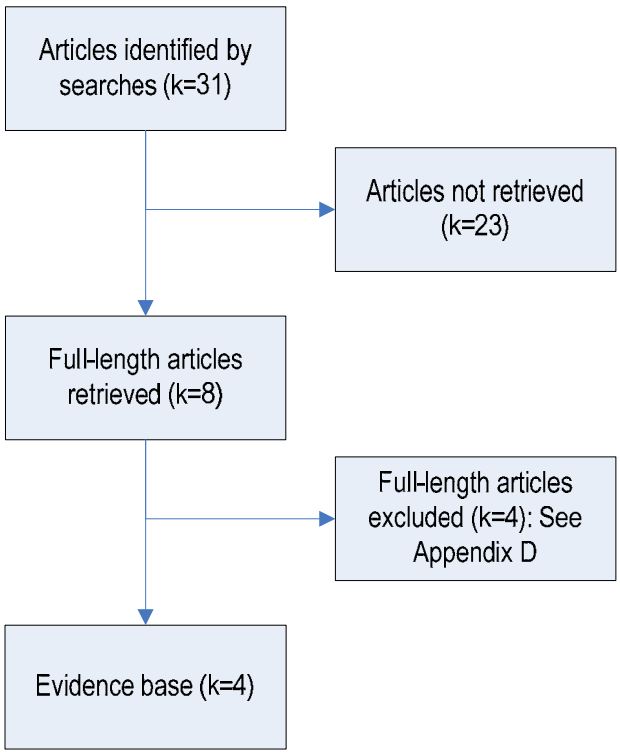


Table 39. Evidence Base for Key Question 8

Reference	Year	Study Location	Country
Menefee et al.(32)	2004	Philadelphia	USA
Saarialho-Kere et al.(17)	1986	Helsinki	Finland
Clark et al.(16)	1986	South Australia	Australia
Forrest et al.(33)	1977	Boston, Bronx, Indianapolis, Los Angeles, Miami and Palo Alto	USA

Evidence Base

This subsection provides a brief description of the key attributes of the four studies that comprise the evidence base for Key Question 8. Here we discuss applicable information pertaining to study design, study quality, and the generalizability of each study's findings to drivers of CMVs. The key attributes of each included study are presented in Table 40.

All four included studies examined the effects on driving ability, cognitive and psychomotor function, and mood and behavior, of combination drug regimens that comprise of a Schedule II drug and any other drug. Drugs that are comprised of the combination of a Schedule III drug with another drug that has the same function to form a single product are not considered in this section. For example, codeine when combined

with ibuprofen (another analgesic) is considered to be a Schedule III drug in its own right.

Of the four included studies, two assessed the effects of combining a Schedule II drug with another drug in healthy individuals following a single dose of the two drugs(16,17), one examined the effects of combining two Schedule II drugs of a different class (an opioid and a stimulant) in patients with postoperative pain,(33) one examined the interaction of two Schedule II drugs (two opioids) in chronic opioid users who were being treated for chronic nonmalignant pain(32).

Three of the four included studies were small (n = 10, 12 and 23)(17,32,34) and one study included 450 patients on the surgical wards of five hospitals.(33) The study of Menefee et al.(32) differed from the other three studies in that it was the only one that was not a RCT. This study was a single arm study that utilized a pre-post study design and compared outcome prior to and following the addition of the Schedule II opioid fentanyl to stable doses of another Schedule II opioid, oxycodone.

Table 40. Key Study Design Characteristics of Studies that Address Key Question 8

Reference	Year	Research question	Drug combination examined	Study Design	Comparison	Outcomes assessed
Long-term opioid use						
Menefee et al.(32)	2004	To evaluate driving performance, cognition, and balance in patients with chronic non-malignant pain before and after the addition of transdermal fentanyl to oxycodone to their treatments	Oxycodone (<15 mg - oral) and transdermal fentanyl	Prospective, one group-pretest-posttest design	23 subjects suffering from nonmalignant pain , taking less than 15 mg equivalent of oxycodone were tested before and after addition of transdermal fentanyl to their treatments	1. Driving simulator 2. Cognitive performance: visual motor tracking/ mental flexibility, memory and attention
ingle-dose studies						
Saarialho-Kere et al.(17)	1986	To study the interaction between narcotics and diazepam	Codeine (100 mg – oral) + diazepam (0.25 mg/ kg)	RCT (double-blind, placebo controlled with crossover)	10 healthy volunteers received pentazocine, codeine, placebo and diazepam at two weeks intervals	1. Objective test: DSST, CFF, Body sway, Maddox wing test, Lateral gaze nystagmus 2. Subjective effects on mood and behavior (VAS)
Clark et al.(16)	1986	To examine the effects on auditory selective attention of methylphenidate and clonidine administered intravenously to normal volunteers	Methylphenidate (0.65 mg/kg - IV) and droperidol (15 µg/kg - IV)	RCT (double-blind, placebo controlled with crossover)	12 right handed male volunteers received each of the following treatments: methylphenidate, droperidol and placebo	1. Dichotic monitoring (divided and focused attention) 2. Subjective state.
Forrest et al.(33)	1977	To examine the clinical utility of dextroamphetamine and morphine together for the treatment of postoperative pain	Opioid and stimulant: Morphine Sulfate (3,6 or 12 mg - IM) and dextroamphetamine (5 or 10 mg - IM)	RCT	450 patients on the surgical wards of five hospitals identified before operation as likely to have severe postoperative pain	1. Three performance tests: 2. Tapping speed, simple arithmetic and symbol copying. 3. Subjective assessments

Quality of Evidence Base

The results of our assessment of the quality of the studies included in the evidence base for Key Question 8 are presented in Table 41.

Table 41. Quality of that Assess Key Question 8

Reference	Year	Quality Scale Used	Quality Score	Quality
Menefee et al.(32)	2004	ECRI Quality Scale III – Pre-Post Studies	7.7	Low
Saarialho-Kere et al.(17)	1986	ECRI Quality Scale I – Comparative Trials with crossover	9.2	High
Clark et al.(16)	1986	ECRI Quality Scale I – Comparative Trials with crossover	8.8	High
Forrest et al.(33)	1977	ECRI Quality Scale I – Comparative Trials	6.2	Moderate

Generalizability of Evidence to Target Population

Important characteristics of the individuals included in the studies that form the evidence base for Key Question 8 are presented in Table 3. None of the included studies enrolled CMV drivers. The individuals enrolled in the studies of Clark et al. and Saarialho et al. tended to be young, healthy male individuals. Consequently, data from these two studies may be generalizable only to a subset of CMV drivers; those aged 20 to 40 who are in very good health. All of the enrollees in the study of Forrest et al. were patients on the surgical wards of five hospitals who had been identified before operation as likely to have severe postoperative pain. It is unlikely that such individuals would be driving large trucks, so the relevance of the findings of this study to CMV drivers is poor. Individuals enrolled in the study of Menefee et al. are fairly representative of the type of individuals who generally use medically indicated opioids in the general population in terms of age and medical condition and so are likely to be reasonably similar to CMV drivers who would be candidates for treatment with opioids. The generalizability of the findings of this latter study is limited, however, by the fact that the proportion of women included in the study is far higher than the proportion of female CMV drivers.

Table 42. Individuals Enrolled in Studies that Address Key Question 8

Reference	Year	Treatment Group	Age distribution	Disease state	Pain level	Length of education	%Male	%White	Driving experience	Generalizability to CMV drivers
Long-term opioid use										
Menefee et al.(32)	2004	n = 23 (pretest-posttest study; patients tested before and after addition of fentanyl to treatment with oxycodone)	Mean: 47 (SD: 10) (Range: 33-67)	Chronic nonmalignant pain	Mean: 67 (SD: 21) VAS	NR	26%	NR	NR	Fair
Single dose studies										
Saarialho-Kere et al.(17)	1986	n = 10 (Crossover – opioid + diazepam vs. placebo)	Rng: 20–26 years	Healthy	No Pain	(Student volunteers)	50%	NR	NR	Unclear
Clark et al.(16)	1986	n = 12 (Crossover-Methylphenidate +droperidol vs placebo)	Range: 18-30 years	Volunteers screened for medical and psychiatric abnormalities and for hearing deficits	NR	NR	100%	NR	NR	Unclear
Forrest et al.(33)	1977	n = 450 0 mg amphetamine with morphine 3mg (48) 60mg (49) 12mg (52) 5mg amphetamine With morphine 3mg (51) 60mg (52) 12mg (52) 10 mg amphetamine With morphine 3mg (50) 60mg (46) 12mg (50)	Mean: 35	Patients on the surgical ward of five hospitals identified before operation as likely to have severe postoperative pain. (Free of major organ-system disease)	NR	NR	99%	NR	NR	Poor

NR = Not reported

Findings

Details on the outcomes of interest addressed by each of the four included studies are presented in Table 43. All four studies examined the effects of interactions between a Schedule II drug and another drug on various measures of cognitive or psychomotor function and one study examined the effects on driving ability as measured using a driving simulator. However, the effect of the drug combinations on mood and behavior was not assessed.

Table 43. Outcomes Assessed by Studies that Address Key Question 8

Reference	Year	Experimental/Simulated Driving	Motor and/ or Cognitive Performances	Mood* or Behavior†
Menefee et al.(32)	2004	√	√	
Saarialho-Kere et al.(17)	1986		√	
Clark et al.(16)	1986		√	
Forrest et al.(33)	1977		√	
Total number of studies =		1	4	0

Simulated/Experimental Driving Ability

Menefee et al.(32) (Quality Score = 7.7: Low) assessed the effects of adding the Schedule II opioid fentanyl to oxycodone (another Schedule II opioid) on simulated driving among individuals with chronic nonmalignant pain. The study did not find any evidence for deterioration in driving ability following the addition of fentanyl to oxycodone.

Cognitive and/or Psychomotor Function

The four included studies utilized a total of 15 different psychometric tests (Table 44). There was no overlap in the instruments that were used across the four studies. Consequently, our assessment of the findings of the four studies that address Key Question 8 is limited to a qualitative assessment of the available evidence.

Table 44. Measures of Cognitive and Psychomotor Function used in Studies that Address Key Question 8

Outcome assessed	Menefee et al.(32) 2004	Saarialho-Kere et al.(17) 1986	Clark et al.(16) 1986	Forrest et al.(33) 1977	Total number of studies
Trail Making Test A & B	√				1
Rey Complex figure test (memory)	√				1
Recognition trial (memory)	√				1
Wechsler Memory Scale III Spatial Span Test (WMS-III)	√				1
Rey Test (Visual and constructional memory)	√				1
d2 Test of attention	√				1

Outcome assessed	Menefee et al.(32) 2004	Saarialho-Kere et al.(17) 1986	Clark et al.(16) 1986	Forrest et al.(33) 1977	Total number of studies
Conner's Continuous Performance Test II (CPT II) (Attention)	√				1
Digit Symbol Substitution		√			1
Flicker Fusion		√			1
Maddox Wing Test		√			1
Lateral Gaze Nystagmus		√			1
Dichotic monitoring			√		1
Tapping speed				√	1
Simple arithmetic				√	1
Symbol copying				√	1

The findings of the four studies that examined the effects of combining another drug to a Schedule II drug on cognitive and/or psychometric function are presented in Table 6.

Effects of combining two Schedule II opioids

Menefee et al.(32) (Quality Score = 7.7: low) examined the effects of adding another Schedule II drug to the drug regimen of individuals already taking a Schedule II drug. This study found that the addition of the Schedule II opioid (fentanyl) to another Schedule II drug (oxycodone) did not have a negative impact on cognitive or psychomotor performance. Rather, performance improvement was observed in some measures of cognitive function. Pain also decreased over the course of treatment and that could explain the improvements in cognition.

Effects of combining two Schedule II drugs of different drug class

Forrest et al.(33) (Quality Score 6.2; moderate) examined the effect of combining a Schedule II opioid (morphine) with a Schedule II stimulant (amphetamine) on cognitive and psychomotor function. The results of this study suggest that any impairment measured after administration of opioid was counteracted by the addition of the stimulant, which also appeared to enhance the analgesic effect of the opioid.

Effects of combining other drugs with a Schedule II drug

Two included studies examined the effects of combining a Schedule II drug with another non-Schedule II drug. Saarialho-Kere et al. (Quality Score = 9.2; high) examined the effects of combining a Schedule II opioid (codeine) with the Schedule IV benzodiazepine, diazepam (Valium®)(17) . Clark et al. (Quality Score = 8.8; high) examined the effects of combining a Schedule II stimulant (methylphenidate) with the unscheduled drug droperidol (Inapsin®)(16) .

Neither study found evidence that interactions between the drugs examined have a negative impact on cognitive or psychomotor function when moderate doses of the drug

are given. However, it was found that both Schedule II drugs counteracted or reversed the effects of the other drugs on subjective performance.

Table 45. Effect of Drug Combinations that Include a Schedule II Drug on Cognitive or Psychomotor Function

Reference	Year	Drug examined	Findings	Conclusions
Long-term opioid use				
Menefee et al.(32)	2004	Opioids: oxycodone (<15 mg, oral) and transdermal fentanyl	There were no significant differences between measures of driving before and during treatment with transdermal fentanyl. No significant decrements in cognitive performance were found. Rather, significant improvements were found in both immediate recall (P <0.01) and 20-minute –delayed recall (P <0.01); Improvements were also found in focus (P <0.001) and attentiveness (P = 0.02) while on transderrmal fentanyl. No differences were found in two tests of balance.	The addition of transdermal fentanyl to the treatment regimen for patients with chronic nonmalignant pain conditions taking up to 15mg oral oxycodone equivalent (i.e., approximately three tablets) per day did not negatively affect driving performance, reaction time, or cognition
Single dose studies				
Saarialho-Kere et al.(17)	1986	Codeine (oral) 100 mg and diazepam (0.25 mg/ kg)	When given after codeine the peak effects of diazepam on scales drowsy / alert (P <0.05), Wilcoxon test) and calm / nervous (P <0.05) appeared later than after placebo + diazepam. Codeine reduced the absorption of diazepam. Codeine counteracted diazepam-induced feeling of impaired performance (Wilcoxon test; P <0.05)	Codeine counteracts the effect of diazepam on subjective performance. The subjects overestimated their performance after opiates + diazepam when compared to diazepam alone
Clark et al.(16)	1986	Methylphenidate (IV) 0.65 mg/kg and droperidol (15 µg / kg)	Methylphenidate had no effects on dichotic monitoring task performance Subjective assessments: Subjects rated themselves more alert (P <0.003). more elated (P = 0.001), less lethargic (P = 0.008) and less depressed in the methylphenidate than the placebo condition. Spontaneous behavior: Subjects made comments such as “feel relax and alert,” “feel good now.” “feel terrific now” and “ready for action”. Four subjects made comments that indicated that following droperidol certain of the subjective effects of methylphenidate were less intense than when methylphenidate was administered alone. For example three subjects mentioned than although they experienced euphoria and talkativeness as before, it lasted for a considerably shorter period. Only 2 subjects commented on the ability to concentrate: both mentioned being easily distracted, and one mentioned losing his train of thought more often than normal though he could “bring himself back” once this was realized. Only one subject commented on perceptual experiences when methylphenidate had reversed the effects of droperidol: “ this (methylphenidate is very much an outlook sensation drug which means you respond to a lot of different things at the same time …I am aware of my scope of vision … trying to take everything in at once”.	Methylphenidate administered 1h after droperidol treatment reversed all signs of withdrawal and depression
Forrest et al.(33)	1977	Morphine Sulfate (3, 6 or 12 mg) and dextroamphetamine (5 or 10 mg) (IM)	Dextroamphetamine adds substantially to the analgesic effect of morphine while offsetting or minimizing other undesirable effects of morphine. Analgesia, as measured by the patients’ subjective responses to questions about relief of pain, was augmented when dextroamphetamine was given with morphine; the combination of dextroamphetamine, 10 mg, with morphine was twice as potent as morphine alone, and the combination with 5 mg was 1½ times as potent as morphine. In simple performance tests, and in measures of side effects, dextroamphetamine generally offset undesirable effects of morphine (sedation and loss of alertness) while increasing analgesia.	Conclusion: Morphine resulted in a dose related impairment on all 3 performance measures. The impairment was counteracted by the addition of dextroamphetamine, which also appeared to enhance the analgesic effect of morphine. The combination resulted in patients being considerably more alert than they would have been with the same analgesic dose of morphine given alone.

Section Summary

A paucity of data precludes one from drawing evidence-based conclusions pertaining to the effect of combining a Schedule II drug with another drug on driving ability, cognitive or psychomotor function, and mood and behavior.

Four relevant studies met the inclusion criteria for this report. Each study evaluated the effects of a different combination of a Schedule II drug with another drug. Because none of these studies were high-quality mega-trials, replication is required before evidence-based conclusions about the effects of combining Schedule II drugs with other drugs can be drawn.

Conclusions

The fact that Schedule II controlled drugs are designed to interfere with neurochemical pathways in the brain would lead one to expect that this may influence ones ability to perform complex tasks such as driving. This expectation, combined with the wealth of incontrovertible evidence showing that individuals who abuse psychotropic drugs are at a significantly increased risk for a motor vehicle crash, leads one to conclude that individuals who take Schedule II controlled drugs for legitimate medical purposes will logically be at increased risk for a motor vehicle crash. The purpose of this evidence report was to determine whether currently available evidence supports the hypothesis that individuals who use Schedule II drugs legally for a legitimate medical condition pose a threat to road traffic safety.

The findings of our assessment, which are based on indirect measures of driving ability, suggest that the use of Schedule II opioids and depressants may indeed pose a threat to road traffic safety when one first begins to use them. Evidence from several studies that administered the drugs to opioid- or depressant-naïve healthy individuals, though not providing strong evidence, have shown that simulated driving ability and high level cognitive and psychomotor function are adversely affected by these drugs.

Evidence from studies of the effects of Schedule II stimulants do not provide evidence that the licit use of these drugs is likely to impact driver safety. However, evidence from several low-quality studies of chronic Schedule II opioid users who use the drugs for the treatment of chronic pain suggests that after a week or two of administration of the opioids at stable therapeutic doses, the adverse effects of the drugs diminish so that measures of the cognitive and psychomotor performance of licit long-term opioid users are indistinguishable from normal. Whether the findings of these studies can legitimately be interpreted as providing evidence that long-term users of stable, therapeutic doses of a Schedule II opioid are at no greater risk for a crash than comparable individuals who are not using the drugs is not at all clear at this time.

Because no studies of the long-term effects of licit Schedule II barbiturate use met the inclusion criteria for this evidence report, we do not know whether the observed short-term detrimental effects of Schedule II barbiturates on driving ability and cognitive and psychomotor function diminish with long-term use.

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Appendix A: Search Summary

The search strategies employed combinations of free text keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. The strategy below is presented in OVID syntax; the search was simultaneously conducted across Embase, Medline, and PsycINFO. A parallel strategy was used to search the databases comprising the Cochrane Library.

Medical Subject Headings (MeSH), Emtree, PsycINFO and Keywords

Conventions:

OVID

$ = truncation character (wildcard)

exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

.de. = limit controlled vocabulary heading

.fs. = floating subheading

.hw. = limit to heading word

.md. = type of methodology (PsycINFO)

.mp. = combined search fields (default if no fields are specified)

.pt. = publication Type

.ti. = limit to title

.tw. = limit to title and abstract fields

PubMed

[mh] = MeSH heading

[majr] = MeSH heading designated as major topic

[pt] = Publication Type

[sb] = Subset of PubMed database (PreMedline, Systematic, OldMedline)

[sh] = MeSH subheading (qualifiers used in conjunction with MeSH headings)

[tiab] = keyword in title or abstract

[tw] = Text word

Embase/Medline/PsycINFO

Set Number	Concept	Search statement
1	Accidents	Accidents, traffic.de. or highway safety.de. or motor traffic accidents.de. or traffic crash.de. or traffic safety.de. or crash$.ti. or wreck$.ti. or collision.ti. or crash$.ti.
2	Driving	Automobile driving.de. or exp motor vehicles/ or automobiles.de. or exp driving behavior/ or exp car driving/ or exp motor vehicle/ or driving.ti.
3	Combine sets	1 or 2
4	Drugs	Exp pharmaceutical preparations/ or exp drug/ or exp drugs/ or exp chemicals and drugs/
5	Opioids	exp Analgesics, opioid/ OR exp narcotics/ OR narcotic$.ti. OR opioid$.ti. OR opiate$.ti. OR Acemethadone OR acetylmethadol OR alfenta OR alfentanil OR amidone OR anileridine OR ardinex OR benzomorphan OR benzomorphans.de. OR buprenorphine OR buprenex OR butorphanol OR carfentanil OR codeine OR codinovo OR delsym OR Demerol OR dextromethorphan OR dextromoramide OR dextrorphan OR dezocine OR diacetyl morphine OR diamorphine OR dicodid OR dihydrocodeinone OR dihydroetorphine OR dihydrohydroxycodeinone OR dihydromorphine OR dihydrone OR dilaudid OR dimepheptanol OR dinarkon OR dionine OR diprenorphine OR dolantin OR dolargan OR dolcontral OR dolophine OR dolosal OR dolsin OR duragesic OR duramorph OR dyhydromorphinone OR dynorphin OR endomorphin OR eseroline OR ethylketocyclazocine.de. OR ethomorphine OR ethorpine OR ethylmorphine OR etorphine OR eucodal OR fenoperidine OR fentanyl OR fioricet OR fortral OR heroin OR hycodan OR hycon OR hydrocodon OR hydrocodone OR hydrocon OR hydromorphon OR hydromorphone OR hydroxycodeinon OR isocodeine OR isonipecain OR isopromedol OR kaolin-pectin OR ketobemidone OR laudacon OR lealgin OR levallorphan OR levamethadyl OR levodroman OR levomethadyl OR levorphane OR levorphanol OR lexir OR lidol OR lorfan OR lofentain OR lydol OR meperidine OR meptazinol OR methadol OR methadone OR methadyl acetate.de. OR moradol OR morphia OR morphine OR morphine derivatives.de. OR MS Contin OR methylnaloxone OR nalbuphine OR naloxiphan OR naloxone OR nocistatin OR noscapine OR nubain OR numorphan OR omnopon OR operidine OR opium OR oramorph OR oxycodeinon OR oxycodone OR oxycone OR oxyconum OR oxycontin OR oxymorphone OR pancodiene OR pantopon OR papaveretum OR paracymethadol OR paramorfan OR paramorphan OR paregoric OR pentazocine OR percocet OR pethidine OR phenadone OR phenazocine OR phenbenzorphan OR phenethylazocine OR phenoperidine OR physeptone OR promedol OR propoxyphene OR protopine OR pyrrolamidol OR rapifen OR remifentanil OR revivon OR robidone OR stadol OR sufentail OR sufentanyl OR talwin OR temgesic OR thebaine OR theocodin OR tilidine OR tramadol OR trimeperidine OR valoron OR valerone OR vicodin
6	Amobarbital	Amobarbital or altinal or alyobarbitone or amal or amatane or amitane or amobarbital sodium or amobarbitone or amsal or amsebarb or amybal or amybarbital or amycal or amydorm or amylbarbitone or amylobarbital or amylobarbitone or amytal or amythal or barbamil or barbamyl or dorlotin or dorlotyn or dorminal or dormital or dormytal or etamyl or eunoctal or hypnamil or inmetal or isoamitil or isomyl or isomytal or isonal or mylodorm or neur amyl or neur-amyl or neuramyl or novamobarb or pentymal or pentymolum or placidel or sodium amital or sodium amobarbital or sodium amylobarbitone or sodium amytal or stadadorm or transital
7	Amphetamine	Amphetamine or actedron or actemin or adderalll or adipan or aktedrin or aktedron or alentol or allodene or amfetamine or amphamed or amphamine or amphetaime or amphetamin or amphetaminyl or amphethamine or amphezamin or anara or astedin or badrin or benzafinyl or benzebar or benzedrine or benzolone or benzpropamin or benzpropamine or beta aminopropylbenzene or betafen or beta phenyl isopropylamine or beta phenylisopropylamine or bluzedrin or centramin or centramina or desoxynorephedrin or diethamine or diethanine or dipan or elastonin or elastonon or euphobine or euphodine or euphodyn or fabedrine or fenamine or fenara or fenedrin or ibiozedrine or isoamin or isoamine or isoamyn or isoamyne or isomyn or levampfetamine or levamphetamine or levedrine or linampheta or mecodrin or mimetina or monetamin or monophos or mydrial or noclon or norephedrane or norphedrane or novydrine or obesin andromacro or obetrol or oktedrin or oraldrina or ortedrine or percomon or pharmamedrine or pharmedrine or phenamin or phendrine or phenoprominum or phenpromin or phenylaminopropane or profamina or profetamine or propisamine or psychedrin or psychedrine or psychoton or racephen or raphetamine or rhinalator or sedolin or simpamina or simpamine or simpatedrin or simpatedrine or stimulan or sympametin or sympamine or sympatedrine or theptine or thyramine or vapedrine or zedrin or zedrine
8	Methamphetamine	Methamphetamine or adipex or ambar or amphedroxyn or benzphetamine or benzfetamine or corvitin or daropervamin or deofed or deoxyephedrine or desamine or desfedrin or desoxo 5 or desoxyephedrine or desoxyfed or desoxyn or destim or desyphed or detrex or dextrim or dexyfed or didrex or doe or doxephrin or doxyfed or drinalfa or effroxine or efroxin or efroxine or esophan or estimulex or eufodrin or eufodrinal or gerovit or hiropon or iosphan or isophen or kemodrin or madrine or metamfetamine or metamphetamine or methamine or methampex or methamphetamin or methamphin or methedrine or methoxyn or methylamphetamine or methylbenzedrine or methoxyn or methylisamin or methylisomyn or methylpropamine or neopharmedrine or normadrine or norodin or norodrin or oxydess or oxydrene or oxyfed or pervitin or philipon or philopon or premodrin or psykoton or semoxydrine or soxysympamine or syndrox or tonedron

Set Number	Concept	Search statement
9	Methylphenidate	Methylphenidate or centedrin or concerta or equasym or metadate or methylfenidate or methylin or methyl phenidate or methylphenidylacetate or methylphenindate or methylphenydate or methypatch or phenidylate or phenidyl hydrochloride or Ritalin or tsentedrin
10	Pentobarbital	Pentobarbital or auropan or barpental or carbrital or diabutal or dorsital or embutal or ethaminal or euthanyl or euthesate or isoamytal or iturate or mebubarbital or mebumal or mebumalum or napental or narcovet or Nembutal or palapent or pentabarbitone sodium or palapent or pentobarbitalum or pentobarbitone or pentone or pentyl or praecicalm or sagatal or sedalixir or sodium ehaminal or somnopentyl or somnotol or sopental or sotyl or vetbutal
11	Secobarbital	Secobarbital or barbosec or bipinal sodium or evronal or guinalbarbital or hypotrol or hyptran or imesonal or immenoctal or meballymal or quinalbarbital or quinal barbitone or quinalbarbitone or quinalspan or sebar or secobarbitone or seconal or seco synatan or sedutain
12	Combine sets	or/4-11
13	Mental function	(exp mental processes/ or exp psychomotor or exp neuropsychological performance/ or performance/ or exp reaction time or exp mental function/ or exp response latency/ or exp cognition/ or exp perceptual motor processes/ or exp psychomotor performance/)
14	Attention	Continuous performance test or road tracking test or divided attention task or eye movement
15	Risk taking	Risk-taking.de. or choice behavior
16	Combine sets	or/13-15
17	Combine sets	12 and (3 or 16)
18	Limit by publication type	17 not ((letter or editorial or news or comment or case reports or review or note or conference paper).de. or (letter or editorial or news or comment or case reports or review).pt.)
19	Eliminate overlap	Remove duplicates from 18
20	Exclude concepts	19 not (an?esthes$.ti. or anesth$.hw. or anaesth$.hw)

General Limiters: English Language, human

Appendix B: Retrieval Criteria

Appendix B will list the retrieval criteria for each of the eight key questions addressed in this report. An example of a small set of retrieval criteria are presented below.

Retrieval Criteria for Key Question 1: Does use of a prescribed Schedule II drug increase the risk for a motor vehicle crash?

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that attempted to determine the risk for a motor vehicle crash either directly (risk for a fatal or non-fatal crash) or indirectly (risk for being stopped for suspicion of driving while intoxicated) associated with the legitimate use of a Schedule II drug.
- Article must describe a study that includes a comparison group comprised of comparable subjects not taking prescribed Schedule II drug.
- Articles describing studies that include individuals taking prescribed methadone as part of a drug-rehabilitation program do not meet the criteria for retrieval for this question.
- Articles describing studies that included individuals taking a Schedule II drug for illicit purposes do not meet the criteria for retrieval for this question.

Retrieval Criteria for Key Question 2: Does use of a prescribed Schedule II drug negatively impact indirect measures of driving ability?

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that attempted to evaluate one of the following indirect measures of driving ability among subjects taking a Schedule II drug for a legitimate purpose:
  - Measures of cognitive function.
  - Measures of psychomotor function
  - Measures of behavior (risk taking behavior, aggression, etc)
  - Measures of driving-related performance (laboratory and experimental)
- Article must describe a study that includes a comparison group comprised of individuals who were not taking prescribed Schedule II drug.
- Article must describe a study that only enrolled subjects taking a Schedule II drug for a legitimate medical purpose.

- Articles that describe studies that included individuals taking prescribed methadone as part of a drug-rehabilitation program do not meet the criteria for retrieval for this question.
- Articles that describe studies that included individuals taking a Schedule II drug for illicit purposes do not meet the criteria for retrieval for this question.

Retrieval Criteria for Key Question 3: What is the correlation between serum level of a Schedule II drug and the risk for a motor vehicle crash?

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that attempted to empirically determine the relationship between serum levels of a Schedule II drug and crash risk

Retrieval Criteria for Key Question 4: What is the correlation between serum level of Schedule II drug and indirect measures of driving ability?

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that attempted to empirically determine the relationship between serum levels of a Schedule II drug and at least one of the following outcomes:
    - Measures of cognitive function.
    - Measures of psychomotor function
    - Measures of behavior (risk taking behavior, aggression, etc)
    - Measures of driving-related performance (laboratory and experimental)

Retrieval Criteria for Key Question 5: Is there a relationship between the pharmacokinetics of a Schedule II drug and the risk for a motor vehicle crash?

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that attempted to empirically evaluate the relationship between the pharmacokinetics (time to peak serum concentration, elimination half-life, bioavailability, etc) of a Schedule II drug and crash risk.

Retrieval Criteria for Key Question 6: Is there a relationship between the pharmacokinetics of a Schedule II drug and indirect measures of driving ability?

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that attempted to empirically evaluate the relationship between the pharmacokinetics (time to peak serum concentration, elimination half-life, bioavailability, etc) of a Schedule II drug and at least one of the following outcomes:
    - Measures of cognitive function
    - Measures of psychomotor function
    - Measures of behavior (risk taking behavior, aggression, etc)
    - Measures of driving-related performance (laboratory and experimental)

Retrieval Criteria for Key Question 7: Are there common drug interactions that include a prescribed Schedule II drug that increase the risk for a motor vehicle crash?

- Article must have been published in the English language.
- Article must have enrolled 10 or more subjects.
- Article must describe a study that attempted to determine crash risk among subjects taking a Schedule II drug for a legitimate medical purpose in combination with another drug (or drugs) commonly used by the population included in the trial. Individuals enrolled in this arm of study must be exposed to the same drug combination.
- Article must describe a study that includes a comparison group comprised of individuals taking the same Schedule II drug as individuals included in the combined drug group.
- Articles that describe studies that included individuals taking prescribed methadone as part of a drug-rehabilitation program do not meet the criteria for retrieval for this question.
- Articles that describe studies that included individuals taking a Schedule II drug for illicit purposes do not meet the criteria for retrieval for this question.
- Article must present motor vehicle crash risk data in a manner that will allow ECRI to calculate (directly or through imputation) effect size estimates and confidence intervals.

Retrieval Criteria for Key Question 8: Are there common drug interactions that include a prescribed Schedule II drug that affect indirect measures of driving ability?

- Article must have been published in the English language.

- Article must have enrolled 10 or more subjects.
- Article must describe a study that attempted to determine crash risk among subjects taking a Schedule II drug for a legitimate medical purpose in combination with another drug (or drugs) commonly used by the population included in the trial. Individuals enrolled in this arm of study must be exposed to the same drug combination.
- Article must describe a study that includes a comparison group comprised of individuals taking the same Schedule II drug as individuals included in the combined drug group.
- Articles that describe studies that included individuals taking prescribed methadone as part of a drug-rehabilitation program do not meet the criteria for retrieval for this question.
- Articles that describe studies that included individuals taking a Schedule II drug for illicit purposes do not meet the criteria for retrieval for this question.
- Article must describe a study that attempted to evaluate the effects of combining a Schedule II drug with other drugs on at least one of the following outcomes:
    - Measures of cognitive function
    - Measures of psychomotor function
    - Measures of behavior (risk taking behavior, aggression, etc)
    - Measures of driving-related performance (laboratory and experimental)

Appendix C: Inclusion Criteria

Appendix C will list the inclusion criteria for each key question. An example of a small set of retrieval criteria are presented below.

Inclusion Criteria for Key Question 1: Does use of a prescribed Schedule II drug increase the risk for a motor vehicle crash?

- Article must have been published in the English language.
- Article must be a full-length article.
- Article published on or following 01/01/1966.
- Article must describe a study that enrolled 10 or more subjects in each study arm.
- Article must describe a study that enrolled individuals aged ≥18 years.
- Article must describe a study that attempted to determine the risk for a motor vehicle crash either directly (risk for a fatal or non-fatal crash) or indirectly (risk for being stopped for suspicion of driving while intoxicated) associated with the legitimate use of a Schedule II drug.
- Article must describe a study that includes a comparison group comprised of comparable subjects not taking prescribed Schedule II drugs.
- Articles describing studies that included individuals taking a Schedule II drug for illicit purposes do not meet the criteria for inclusion for this question.
- Articles describing studies that include individuals taking prescribed methadone as part of a drug-rehabilitation program do not meet the criteria for inclusion for this question.
- Article must present motor vehicle crash risk data in a manner that will allow ECRI to calculate (directly or through imputation) effect size estimates and confidence intervals.

Inclusion Criteria for Key Question 2: Does use of a prescribed Schedule II drug negatively impact indirect measures of driving ability?

- Article must have been published in the English language.
- Article published on or following 01/01/1966.
- Article must describe a study that enrolled 10 or more subjects in each study arm.
- Article must describe a study that enrolled individuals aged ≥18 years.
- Article must describe a study with a follow-up time of >24 hours.
- Article must describe a study in which more than a single dose of drug is administered (i.e., study is not a pharmacokinetics study).

- Article must describe a study that attempted to evaluate one of the following indirect measures of driving ability among subjects taking a Schedule II drug for a legitimate purpose:
  - Measures of cognitive function.
  - Measures of psychomotor function
  - Measures of behavior (risk taking behavior, aggression, etc)
  - Measures of driving-related performance (laboratory and experimental)
- Article must describe a study that includes a comparison group comprised of individuals who were not taking prescribed Schedule II drugs.
- Articles describing studies that included individuals taking a Schedule II drug for illicit purposes do not meet the criteria for inclusion for this question.
- Articles describing studies that include individuals taking prescribed methadone as part of a drug-rehabilitation program do not meet the criteria for inclusion for this question.
- Article must present outcome data in a manner that will allow ECRI to calculate (directly or through imputation) effect size estimates and confidence intervals.

Inclusion Criteria for Key Question 3: What is the correlation between serum level of a Schedule II drug and the risk for a motor vehicle crash?

- Article must have been published in the English language.
- Article must be a full-length article.
- Article published on or following 01/01/1966.
- Article must describe a study that enrolled 10 or more subjects in each study arm.
- Article must describe a study that enrolled individuals aged ≥18 years.
- Article must describe a study that attempted to empirically determine the relationship between serum levels of a Schedule II drug and crash risk

Inclusion Criteria for Key Question 4: What is the correlation between serum level of Schedule II drug and indirect measures of driving ability?

- Article must have been published in the English language.
- Article must be a full-length article.
- Article published on or following 01/01/1966.
- Article must describe a study that enrolled 10 or more subjects in each study arm.
- Article must describe a study that enrolled individuals aged ≥18 years.

- Article must describe a study that attempted to empirically determine the relationship between serum levels of a Schedule II drug and at least one of the following outcomes:
    - Measures of cognitive function.
    - Measures of psychomotor function
    - Measures of behavior (risk taking behavior, aggression, etc)
    - Measures of driving-related performance (laboratory and experimental)
- Article must present outcome data in a manner that will allow ECRI to calculate (directly or through imputation) effect size estimates and confidence intervals.

Inclusion Criteria for Key Question 5: Is there a relationship between the pharmacokinetics of a Schedule II drug and the risk for a motor vehicle crash?

- Article must have been published in the English language.
- Article must be a full-length article.
- Article published on or following 01/01/1966.
- Article must describe a study that enrolled 10 or more subjects in each study arm.
- Article must describe a study that enrolled individuals aged ≥18 years.
- Article must describe a study that attempted to empirically evaluate the relationship between the pharmacokinetics (time to peak serum concentration, elimination half-life, bioavailability, etc) of a Schedule II drug and crash risk.
- Article must present outcome data in a manner that will allow ECRI to calculate (directly or through imputation) effect size estimates and confidence intervals.

Inclusion Criteria for Key Question 6: Is there a relationship between the pharmacokinetics of a Schedule II drug and indirect measures of driving ability?

- Article must have been published in the English language.
- Article must be a full-length article.
- Article published on or following 01/01/1966.
- Article must describe a study that enrolled 10 or more subjects in each study arm.
- Article must describe a study that enrolled individuals aged ≥18 years.
- Article must describe a study that attempted to empirically evaluate the relationship between the pharmacokinetics (time to peak serum concentration, elimination half-life, bioavailability, etc) of a Schedule II drug and at least one of the following outcomes:
    - Measures of cognitive function
    - Measures of psychomotor function

    - Measures of behavior (risk taking behavior, aggression, etc)
    - Measures of driving-related performance (laboratory and experimental)
- Article must present outcome data in a manner that will allow ECRI to calculate (directly or through imputation) effect size estimates and confidence intervals.

Inclusion Criteria for Key Question 7: Are there common drug interactions that include a prescribed Schedule II drug that increase the risk for a motor vehicle crash?

- Article must have been published in the English language.
- Article must be a full-length article.
- Article published on or following 01/01/1966.
- Article must describe a study that enrolled 10 or more subjects in each study arm.
- Article must describe a study that enrolled individuals aged ≥18 years.
- Article must describe a study that attempted to determine crash risk among subjects taking a Schedule II drug for a legitimate medical purpose in combination with another drug (or drugs) commonly used by the population included in the trial. Individuals enrolled in this arm of study must be exposed to the same drug combination.
- Article must describe a study that includes a comparison group comprised of individuals taking the same Schedule II drug as individuals included in the combined drug group.
- Articles that describe studies that included individuals taking prescribed methadone as part of a drug-rehabilitation program do not meet the criteria for retrieval for this question.
- Articles that describe studies that included individuals taking a Schedule II drug for illicit purposes do not meet the criteria for retrieval for this question.
- Article must present motor vehicle crash risk data in a manner that will allow ECRI to calculate (directly or through imputation) effect size estimates and confidence intervals.
- Article must present outcome data in a manner that will allow ECRI to calculate (directly or through imputation) effect size estimates and confidence intervals.

Inclusion Criteria for Key Question 8: Are there common drug interactions that include a prescribed Schedule II drug that affect indirect measures of driving ability?

- Article must have been published in the English language.
- Article must be a full-length article.
- Article published on or following 01/01/1966.
- Article must describe a study that enrolled 10 or more subjects in each study arm.

- Article must describe a study that enrolled individuals aged ≥18 years.
- Article must describe a study that attempted to determine crash risk among subjects taking a Schedule II drug for a legitimate medical purpose in combination with another drug (or drugs) commonly used by the population included in the trial. Individuals enrolled in this arm of study must be exposed to the same drug combination.
- Article must describe a study that includes a comparison group comprised of individuals taking the same Schedule II drug as individuals included in the combined drug group.
- Articles that describe studies that included individuals taking prescribed methadone as part of a drug-rehabilitation program do not meet the criteria for retrieval for this question.
- Articles that describe studies that included individuals taking a Schedule II drug for illicit purposes do not meet the criteria for retrieval for this question.
- Article must describe a study that attempted to evaluate the effects of combining a Schedule II drug with other drugs on at least one of the following outcomes:
    - Measures of cognitive function
    - Measures of psychomotor function
    - Measures of behavior (risk taking behavior, aggression, etc)
    - Measures of driving-related performance (laboratory and experimental)
- Article must present outcome data in a manner that will allow ECRI to calculate (directly or through imputation) effect size estimates and confidence intervals.

Appendix D: Excluded Articles

Table D-1. Excluded studies (Key Question 1)

Reference	Year	Reason for Exclusion
Augesberger et al.(35)	2005	Includes data from drug abusers–data from licit users and illicit users not separated
Chowaniec et al.(36)	2005	Did not separate licit from illicit drug use
Hausken et al.(37)	2005	Not relevant-Death rates among individuals who had received a DUI
Jones et al.(38)	2005	Did not separate licit from illicit drug use
Jones et al.(39)	2005	Did not separate licit from illicit drug use
Jones et al.(40)	2005	Study of crash risk among drug abusers
Jones et al.(40)	2005	Drug abusers
Raes et al.(41)	2005	Did not separate licit from illicit drug use
Smink et al.(42)	2005	Did not separate licit from illicit drug use
Toennes et al.(43)	2005	Did not separate licit from illicit drug use
Vaez et al.(44)	2005	Did not separate licit from illicit drug use
Drummer et al.(45)	2004	Did not separate licit from illicit drug use
Movig et al.(46)	2004	Did not separate licit from illicit drug use
Bachs et al.(47)	2003	Not a study of crash. Looks at DUI offenses.
Drummer et al.(48)	2003	Did not separate licit from illicit drug use
Meissner et al.(49)	2002	Drug abusers
Jonassen et al.(50)	2000	Did not separate licit from illicit drug use
Christophersen et al.(51)	1999	Did not separate licit from illicit drug use
Ledingham et al.(52)	1999	Did not separate licit from illicit drug use
Christopherson et al.(53)	1997	Did not separate licit from illicit drug use
Johansson et al.(54)	1997	Not limited to Schedule II drugs and risk data pertaining to Schedule II drugs not presented separately.
Marquet et al.(55)	1997	Did not separate licit from illicit drug use
Leveille et al.(56)	1994	Not limited to Schedule II drugs and risk data pertaining to Schedule II drugs not presented separately.
Gjerde et al.(57)	1993	Did not separate licit from illicit drug use

Reference	Year	Reason for Exclusion
Stoduto et al.(58)	1993	Did not separate licit from illicit drug use
Ray et al.(59)	1992	Not limited to Schedule II drugs and risk data pertaining to Schedule II drugs not presented separately.
Starmer et al.(60)	1992	Did not separate licit from illicit drug use
Christensen et al.(61)	1990	Not limited toSchedule II drugs and risk data pertaining to Schedule II drugs not presented separately.
Budd et al.(62)	1989	Study of crash risk among drug abusers
Lesch et al.(63)	1989	Not limited to Schedule II drugs and risk data pertaining to Schedule II drugs not presented separately.
Lund et al.(64)	1988	Did not separate licit from illicit drug use
Starmer et al.(65)	1988	Did not separate licit from illicit drug use
Bjorneboe et al.(66)	1987	Did not separate licit from illicit drug use
Cosby et al.(67)	1986	Did not separate licit from illicit drug use
Fortenberry et al.(68)	1986	Did not separate licit from illicit drug use
Williams et al.(69)	1985	Did not separate licit from illicit drug use
Wilson et al.(70)	1985	Not limited to Schedule II drugs and risk data pertaining to Schedule II drugs not presented separately.
Mason et al.(71)	1984	Did not separate licit from illicit drug use
Owens et al.(72)	1983	Did not separate licit from illicit drug use
Cimbura et al.(73)	1982	Did not separate licit from illicit drug use
Goldberg et al.(74)	1981	Did not separate licit from illicit drug use
White et al.(75)	1981	Did not separate licit from illicit drug use
Honkanen et al.(76)	1980	Not limited to Schedule II drugs and risk data pertaining to Schedule II drugs not presented separately.
Robinson et al.(77)	1979	Did not separate licit from illicit drug use
Garriott et al.(78)	1976	Not limited to Schedule II drugs and risk data pertaining to Schedule II drugs not presented separately.
Smart et al.(79)	1976	Study of crash risk among drug abusers
Turk et al.(80)	1974	Did not separate licit from illicit drug use
Jamison et al.(81)	1973	Did not separate licit from illicit drug use
Gupta et al.(82)	1966	Not relevant-looks at incidence of barbiturate related death in Ontario.

Table D-2. Excluded studies (Key Question 2)

Reference	Year	Reason for Exclusion
Cox et al.(83)	2004	Sample too young–≤18 years old
Cox et al.(84)	2004	Insufficient patient number ≤10 patients per study arm
Menefee et al.(32)	2004	Does not compare outcomes with those obtained from a comparable control group
Jamison et al.(85)	2003	Does not compare outcomes with those obtained from a comparable control group
Cox et al.(84)	2000	Insufficient patient number ≤10 patients per study arm
Galski et al.(86)	2000	Inappropriate control-compared opioid users with cerebrally compromised individuals.
Hill et al.(87)	2000	Includes data from drug abusers–data from licit users and illicit users not separated
Sjogren et al.(88)	2000	Mix of Schedule I and II drugs–Data for Schedule II drug users not presented separately
Haythornthwaite et al.(89)	1998	Does not compare outcomes with those obtained from a comparable control group
Lorenz et al.(90)	1997	Insufficient patient number ≤10 patients per study arm
Mintzer et al.(91)	1997	Insufficient patient number ≤10 patients per study arm
Pickworth et al.(92)	1997	Insufficient patient number ≤10 patients per study arm
Meador et al.(93)	1995	Does not compare outcomes with those obtained from a comparable control group
Weitzner et al.(94)	1995	Insufficient patient number ≤10 patients per study arm
Zawertailo et al.(95)	1995	Enrollees were drug abusers
Callaway et al.(96)	1994	Not relevant–modelling study
Sjogren et al.(97)	1994	Mix of Schedule I and II drugs–Data for Schedule II drug users not presented separately
Zacny et al.(98)	1994	Includes data from drug abusers–data from licit users and illicit users not separated
Mitler et al.(99)	1993	Insufficient patient number ≤10 patients per study arm
Veselis et al.(100)	1993	Abstract + Insufficient patient number ≤10 patients per study arm
Westerling et al.(31)	1993	Pharmacokinetics study–FUT less than 24 hours
Blom et al.(101)	1992	Opioid but not Schedule II
Meneely et al.(102)	1992	Insufficient patient number ≤10 patients per study arm
Sellers et al.(103)	1992	Enrollees were drug abusers
Zacny et al.(104)	1992	Pharmacokinetics study–FUT less than 24 hours
Zacny et al.(105)	1992	Pharmacokinetics study–FUT less than 24 hours

Reference	Year	Reason for Exclusion
Hindmarsh et al.(106)	1991	(effect size estimates calculated ranked-no direct comparison).pdf
Banning et al.(107)	1990	Mix of Schedule I and II drugs–Data for Schedule II drug users not presented separately
Meador et al.(108)	1990	Does not compare outcomes with those obtained from a comparable control group
Bruera et al.(109)	1989	Does not compare outcomes with those obtained from a comparable control group
Mortimer et al.(110)	1989	Opioid (dextromorphan) but not Schedule II drug
Saarialho-Kere et al.(111)	1989	Insufficient patient number ≤10 patients per study arm
Sjogren et al.(112)	1989	Mix of Schedule I and II drugs–Data for Schedule II drug users not presented separately
Higgins et al.(113)	1988	Insufficient patient number ≤10 patients per study arm
Saarialho-Kere et al.(114)	1988	Pharmacokinetics study–FUT less than 24 hours + Insufficient patient number ≤10 patients per study arm
Manner et al.(115)	1987	Insufficient patient number ≤10 patients per study arm
Siever et al.(116)	1987	Insufficient patient number ≤10 patients per study arm
Stevenson et al.(117)	1986	Insufficient patient number ≤10 patients per study arm
Bourke et al.(118)	1984	Insufficient patient number ≤10 patients per study arm
Scamman et al.(119)	1984	Insufficient patient number ≤10 patients per study arm
Griffiths et al.(120)	1983	Does not compare outcomes with those obtained from a comparable control group
Callaway et al.(34)	1982	Enrollees ≤18 years
Desjardans et al.(121)	1982	Abstract
Shaywitz et al.(122)	1982	Abstract
Zahn et al.(123)	1981	No outcome of interest examined
Peloquin et al.(124)	1980	Abstract
Evans et al.(125)	1977	No outcome of interest studied
Levine et al.(126)	1976	Insufficient patient number ≤10 patients per study arm
Lombardo et al.(127)	1976	Includes data from drug abusers–data from licit users and illicit users not separated
Stoller et al.(128)	1976	Insufficient patient number ≤10 patients per study arm
Borland et al.(129)	1975	Insufficient patient number ≤10 patients per study arm
Linnoila et al.(130)	1973	Abstract

Table D-3. Excluded studies (Key Question 3)

Reference	Year	Reason for Exclusion
Augesberger et al.(35)	2005	Includes data from drug abusers–data from licit users and illicit users not separated
Chowaniec et al.(36)	2005	Did not separate licit from illicit drug use
Hausken et al.(37)	2005	Not relevant-Death rates among individuals who had received a DUI
Jones et al.(38)	2005	Did not separate licit from illicit drug use
Jones et al.(39)	2005	Did not separate licit from illicit drug use
Jones et al.(40)	2005	Study of crash risk among drug abusers
Jones et al.(40)	2005	Drug abusers
Raes et al.(41)	2005	Did not separate licit from illicit drug use
Smink et al.(42)	2005	Did not separate licit from illicit drug use
Toennes et al.(43)	2005	Did not separate licit from illicit drug use
Vaez et al.(44)	2005	Did not separate licit from illicit drug use
Drummer et al.(45)	2004	Did not separate licit from illicit drug use
Movig et al.(46)	2004	Did not separate licit from illicit drug use
Bachs et al.(47)	2003	Not a study of crash. Looks at DUI offenses.
Drummer et al.(48)	2003	Did not separate licit from illicit drug use
Meissner et al.(49)	2002	Drug abusers
Jonassen et al.(50)	2000	Did not separate licit from illicit drug use
Christophersen et al.(51)	1999	Did not separate licit from illicit drug use
Ledingham et al.(52)	1999	Did not separate licit from illicit drug use
Christopherson et al.(53)	1997	Did not separate licit from illicit drug use
Johansson et al.(54)	1997	Not limited to Schedule II drugs and risk data pertaining toSchedule II drugs not presented separately.
Marquet et al.(55)	1997	Did not separate licit from illicit drug use
Leveille et al.(56)	1994	Not limited to Schedule II drugs and risk data pertaining to Schedule II drugs not presented separately.
Gjerde et al.(57)	1993	Did not separate licit from illicit drug use
Stoduto et al.(58)	1993	Did not separate licit from illicit drug use
Ray et al.(59)	1992	Not limited to Schedule II drugs and risk data pertaining to Schedule II drugs not presented separately.

Reference	Year	Reason for Exclusion
Starmer et al.(60)	1992	Did not separate licit from illicit drug use
Christensen et al.(61)	1990	Not limited to Schedule II drugs and risk data pertaining toSchedule II drugs not presented separately.
Budd et al.(62)	1989	Study of crash risk among drug abusers
Lesch et al.(63)	1989	Not limited to Schedule II drugs and risk data pertaining to Schedule II drugs not presented separately.
Lund et al.(64)	1988	Did not separate licit from illicit drug use
Starmer et al.(65)	1988	Did not separate licit from illicit drug use
Bjorneboe et al.(66)	1987	Did not separate licit from illicit drug use
Cosby et al.(67)	1986	Did not separate licit from illicit drug use
Fortenberry et al.(68)	1986	Did not separate licit from illicit drug use
Williams et al.(69)	1985	Did not separate licit from illicit drug use
Wilson et al.(70)	1985	Not limited to Schedule II drugs and risk data pertaining to Schedule II drugs not presented separately.
Mason et al.(71)	1984	Did not separate licit from illicit drug use
Owens et al.(72)	1983	Did not separate licit from illicit drug use
Cimbura et al.(73)	1982	Did not separate licit from illicit drug use
Goldberg et al.(74)	1981	Did not separate licit from illicit drug use
White et al.(75)	1981	Did not separate licit from illicit drug use
Honkanen et al.(76)	1980	Not limited to Schedule II drugs and risk data pertaining toSchedule II drugs not presented separately.
Robinson et al.(77)	1979	Did not separate licit from illicit drug use
Garriott et al.(78)	1976	Not limited to Schedule II drugs and risk data pertaining to Schedule II drugs not presented separately.
Smart et al.(79)	1976	Study of crash risk among drug abusers
Turk et al.(80)	1974	Did not separate licit from illicit drug use
Jamison et al.(81)	1973	Did not separate licit from illicit drug use
Gupta et al.(82)	1966	Not relevant-looks at incidence of barbiturate related death in Ontario.

Table D-4. Excluded studies (Key Question 4)

Reference	Year	Reason for Exclusion
Byas-Smith et al.(6)	2005	Does not provide evidence relevant to key question
Cox et al.(83)	2004	Sample too young–≤18 years old
Cox et al.(84)	2004	Insufficient patient number ≤10 patients per study arm
Menefee et al.(32)	2004	Does not compare outcomes with those obtained from a comparable control group
Jamison et al.(85)	2003	Does not compare outcomes with those obtained from a comparable control group
Sabatowski et al.(8)	2003	Does not provide evidence relevant to key question
Cox et al.(84)	2000	Insufficient patient number ≤10 patients per study arm
Galski et al.(86)	2000	Inappropriate control-compared opioid users with cerebrally compromised individuals.
Hill et al.(87)	2000	Includes data from drug abusers–data from licit users and illicit users not separated
Sjogren et al.(88)	2000	Mix of Schedule I and II drugs–Data for Schedule II drug users not presented separately
Sjogren et al.(10)	2000	Does not provide evidence relevant to key question
Haythornthwaite et al.(89)	1998	Does not compare outcomes with those obtained from a comparable control group
Lorenz et al.(90)	1997	Insufficient patient number ≤10 patients per study arm
Mintzer et al.(91)	1997	Insufficient patient number ≤10 patients per study arm
Pickworth et al.(92)	1997	Insufficient patient number ≤10 patients per study arm
Moulin et al.(11)	1996	Does not provide evidence relevant to key question
Meador et al.(93)	1995	Does not compare outcomes with those obtained from a comparable control group
Vaino et al.(12)	1995	Does not provide evidence relevant to key question
Weitzner et al.(94)	1995	Insufficient patient number ≤10 patients per study arm
Zawertailo et al.(95)	1995	Enrollees were drug abusers
Callaway et al.(96)	1994	Not relevant–modeling study
Coda et all.(13)	1994	Does not provide evidence relevant to key question
Sjogren et al.(97)	1994	Mix of Schedule I and II drugs–Data for Schedule II drug users not presented separately
Zacny et al.(98)	1994	Includes data from drug abusers–data from licit users and illicit users not separated
Mitler et al.(99)	1993	Insufficient patient number ≤10 patients per study arm
Veselis et al.(100)	1993	Abstract + Insufficient patient number ≤10 patients per study arm
Westerling et al.(31)	1993	Pharmacokinetics study–FUT less than 24 hours
Blom et al.(101)	1992	Opioid but not Schedule II
Meneely et al.(102)	1992	Insufficient patient number ≤10 patients per study arm
Sellers et al.(103)	1992	Enrollees were drug abusers
Zacny et al.(104)	1992	Pharmacokinetics study–FUT less than 24 hours
Zacny et al.(105)	1992	Pharmacokinetics study–FUT less than 24 hours
Hindmarsh et al.(106)	1991	Effect size estimates calculated ranked-no direct comparison
Kerr et al.(14)	1991	Does not provide evidence relevant to key question
Banning et al.(107)	1990	Mix of Schedule I and II drugs–Data for Schedule II drug users not presented separately
Meador et al.(108)	1990	Does not compare outcomes with those obtained from a comparable control group
Bruera et al.(109)	1989	Does not compare outcomes with those obtained from a comparable control group
Mortimer et al.(110)	1989	Opioid (dextromorphan) but not Schedule II drug

Reference	Year	Reason for Exclusion
Saarialho-Kere et al.(111)	1989	Insufficient patient number ≤10 patients per study arm
Sjogren et al.(112)	1989	Mix of Schedule I and II drugs–Data for Schedule II drug users not presented separately
Higgins et al.(113)	1988	Insufficient patient number ≤10 patients per study arm
Saarialho-Kere et al.(114)	1988	Pharmacokinetics study–FUT less than 24 hours + Insufficient patient number ≤10 patients per study arm
Manner et al.(115)	1987	Insufficient patient number ≤10 patients per study arm
Siever et al.(116)	1987	Insufficient patient number ≤10 patients per study arm
Saarialho-Kere et al.(17)	1986	Does not provide evidence relevant to key question
Stevenson et al.(117)	1986	Insufficient patient number ≤10 patients per study arm
Bourke et al.(118)	1984	Insufficient patient number ≤10 patients per study arm
Gualtieri et al.(131)	1984	Sample too young ≤18 years old
Logsdon et al.(18)	1984	Does not provide evidence relevant to key question
Scamman et al.(119)	1984	Insufficient patient number ≤10 patients per study arm
Griffiths et al.(120)	1983	Does not compare outcomes with those obtained from a comparable control group
Callaway et al.(34)	1982	Enrollees ≤18 years
Desjardans et al.(121)	1982	Abstract
Redpath et al.(19)	1982	Does not provide evidence relevant to key question
Shaywitz et al.(122)	1982	Abstract
Zahn et al.(123)	1981	No outcome of interest examined
Peloquin et al.(124)	1980	Abstract
Pishkin et al.(20)	1980	Does not provide evidence relevant to key question
Hindmarch et al.(21)	1979	Does not provide evidence relevant to key question
Tansella et al.(22)	1979	Does not provide evidence relevant to key question
Evans et al.(125)	1977	No outcome of interest studied
Levine et al.(126)	1976	Insufficient patient number ≤10 patients per study arm
Lombardo et al.(127)	1976	Includes data from drug abusers–data from licit users and illicit users not separated
Stoller et al.(128)	1976	Insufficient patient number ≤10 patients per study arm
Borland et al.(129)	1975	Insufficient patient number ≤10 patients per study arm
Ghoneim et al.(23)	1975	Does not provide evidence relevant to key question
Kortilla et al.(24)	1975	Does not provide evidence relevant to key question
Kopriva et al.(25)	1974	Does not provide evidence relevant to key question
Linnoila et al.(26)	1973	Does not provide evidence relevant to key question
Linnoila et al.(130)	1973	Abstract
Betts et al.(27)	1972	Does not provide evidence relevant to key question
Malpas et al.(29)	1970	Does not provide evidence relevant to key question

Table D-5. Excluded studies (Key Question 5)

Reference	Year	Reason for Exclusion
Zacny et al.(104)	1992	Pharmacokinetics study–FUT less than 24 hours
Zacny et al.(105)	1992	Sample too small–<10 pts per arm
Kirk et al.(132)	1990	Sample too small–<10 pts per arm
Barzaghi et al.(133)	1989	Sample too small–<10 pts per arm
Saarialho-Kere et al.(114)	1988	Not a Schedule II drug
Scott et al.(134)	1986	No outcomes of interest
Gualitien et al.(131)	1984	Sample too young–≤18 years old
Scamman et al.(119)	1984	Sample too small–<10 pts per arm
Tedeschi et al.(135)	1983	Sample too small–<10 pts per arm
Evans et al.(125)	1977	No outcomes of interest
Hindmarsh et al.(136)	1975	Sample too small–<10 pts per arm

Table D-6. Excluded studies (Key Question 6)

Reference	Year	Reason for Exclusion
Evans et al.(125)	1977	Does not examine an outcome of interest
Gualitien et al.(131)	1984	Study enrollees too young ≤18 years of age
Zacny et al.(104)	1992	FUT less than 24 hours)-PK
Zacny et al.(105)	1992	Study too small-less than 10 pts per arm
Saarialho-Kere et al.(114)	1988	Not a study of a Schedule II drug
Scott et al.(134)	1986	Does not examine an outcome of interest
Scamman et al.(119)	1984	Study too small-less than 10 pts per arm
Kirk et al.(132)	1990	Study too small-less than 10 pts per arm
Barzaghi et al.(133)	1989	Study too small-less than 10 pts per arm
Tedeschi et al.(135)	1983	Study too small-less than 10 pts per arm
Hindmarch et al.(136)	1975	Study too small-less than 10 pts per arm

Table D-7. Excluded studies (Key Question 8)

Reference	Year	Reason for Exclusion
Jasinski et al.(137)	1986	Subjects were substance abusers
Ivy et al.(138)	1944	Article published in 1944
Cooper et al.(139)	1989	Sample too small–<10 pts per arm
Dalton et al.(140)	1975	Marijuana and placebo vs marijuana and secobarbital

Appendix E: Determining the Stability and Strength of a Body of Evidence

As stated in the main text, ECRI evidence reports differ substantially from other systematic review in that we provide two types of conclusion; qualitative conclusions and quantitative conclusions. In order to reach these conclusions we use an algorithm developed by ECRI to guide the conduct and interpretation of the analyses performed during the development of this evidence report. The algorithm, which is presented in Figure E-3 through Figure E-6, formalizes the process of systematic review by breaking the process down into several discrete steps. At each step, rules are applied that determine the next step in the systematic review process and ultimately to the stability and strength of evidence ratings that are allocated to our conclusions. Because the application of the rules governing each step in the algorithm (henceforth called a decision point) guide the conduct of the systematic review process and how its findings are interpreted, much time and effort was spent in ensuring that the rules and underlying assumptions for each decision point were reasonable.

The algorithm is comprised of three distinct sections: a *General* section, a *Quantitative* section, and a *Qualitative* section. Each of these sections, the decision points that fall within them, and the decision rules that were applied at each step in the present evidence report are described below.

Decision Point 1: Acceptable Quality?

Decision Point 1 serves two purposes: 1) to assess the quality of each included study; 2) to provide a means of excluding studies that are so prone to bias that their reported results cannot be considered useful. To aid in assessing the quality of each of the studies included in this evidence report, we used two study quality assessment instruments. The choice of which instrument to use was based on the design of the study used to address the key questions of interest. In this evidence report we used the ECRI Quality Scale I (for randomized and non-randomized comparative studies), ECRI Quality Scale II (for randomized and non-randomized comparative studies with crossover), the ECRI Quality Scale III (for pre-post studies) and a revised version of the Newcastle-Ottawa Quality Assessment Scale (for case-control studies).(141) These instruments are presented in Appendix F.

Decision Point 2: Determine Quality of Evidence Base

We classified the overall quality of each key question specific evidence base into one of three distinct categories; high, moderate or low quality. Decisions about the quality of each evidence base were based on data obtained using the quality assessment instruments described above using the criteria presented in Table E-1.

Table E-1. Criteria Used to Categorize Quality of Evidence Base

Category	Median EQS I Score	Median EQS III Score	Median EQS III Score	Median NOQAS Score
High Quality	≥8.0	≥8.0		
Moderate Quality	6.0 to 7.9	6.0 to 7.9	≥9.0	≥8.0
Low Quality	≤6.0	≤6.0	<9.0	<8.0

Note that it is not possible for an evidence base consisting of case-control trials to be categorized as high quality. This is the consequence of the fact that this study design can never be protected from potential bias.

Decision Point 3: Quantitative Analysis Performed?

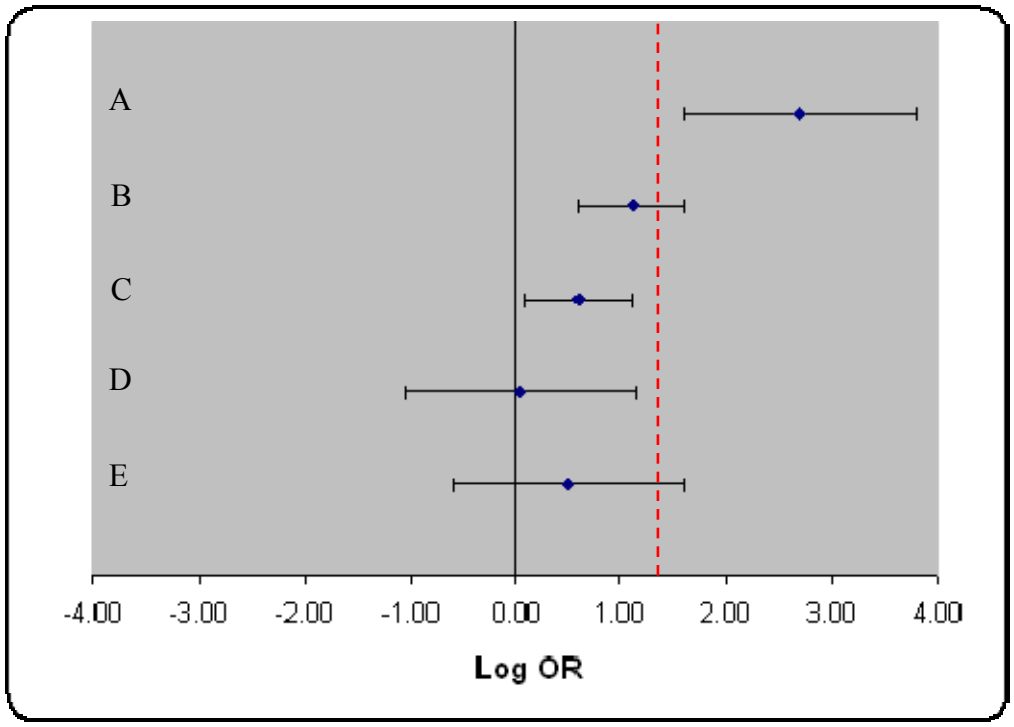
In this evidence report the answer to Decision Point 3 depended on a number of factors; the number of available studies and the adequacy of reporting of study findings. For any given question, combinable data from at least 3 studies must be available before a quantitative analysis will be considered. If 4 or more studies were available but poor reporting precluded ECRI from directly computing relevant effect size estimates for >75% of the available studies, no quantitative analysis were performed. If no quantitative analyses were performed, we moved directly to Decision Point 8 which deals with the assessment of the available evidence with the aim of drawing a purely qualitative conclusion.

Decision Point 4: Are Data Quantitatively Consistent (Homogeneous)?

This decision point was used only when the answer to Decision Point 3 was affirmative and a quantitative analysis was performed. Quantitative consistency refers to the extent to which the quantitative results of different studies are in agreement. The more consistent the evidence, the more precise a summary estimate of treatment effect derived from an evidence base will be. Quantitative consistency refers to consistency tested in a meta-analysis using a test of homogeneity. For this evidence report we used both the Q-statistic and Higgins and Thompson's I^2 statistic.(142) By convention, we considered an evidence base as being quantitatively consistent when I^2 <50% and $P(Q)$ >0.10.

If the findings of the studies included were homogeneous (I^2 <50% and $P(Q)$ >0.10), we obtained a summary effect size estimate by pooling the results of these studies using fixed-effects meta-analysis (FEMA). Having obtained a summary effect size estimate, we then determined whether this estimate effect size estimate was informative. That is, we determined whether the findings of the meta-analysis allowed a conclusion to be drawn. To see what is meant by this, consider Figure E-1. Four of the findings in this figure are informative (A to D). Only finding E is non-informative.

Figure E-1. Informative Findings



Dashed Line = Threshold for a clinically significant difference

Finding A shows that the treatment effect is statistically significant and clinically important. Finding B shows that the treatment effect is statistically significant but it is unclear whether this treatment effect is clinically important. Finding C shows that the treatment effect is statistically significant but that the treatment effect is too small to be considered clinically important. Finding D shows that it is unclear whether there is a statistically important treatment effect, but regardless, this treatment effect is not clinically important. Finding E shows that it is unclear whether there is a statistically important treatment effect and it is also unclear whether the treatment effect is clinically important. This latter finding is thus non-informative.

Decision Point 5: Are Findings Stable (Quantitatively Robust)?

If the findings of the fixed-effects meta-analysis were found to be informative, we next assessed the stability of the summary effect size estimate obtained. Stability refers to the likelihood that a summary effect estimate will be substantially altered by changing the underlying assumptions of the analysis. Analyses that are used to test the stability of an effect size estimate are known as sensitivity analyses. Clearly, ones confidence in the validity of a treatment effect estimate will be greater if sensitivity analyses fail to significantly alter the summary estimate of treatment effect.

For this evidence report, we utilized four different sensitivity analyses. These sensitivity analyses are:

1. *Random-effects meta-analysis of complete evidence base.* When the quantitative analysis is performed on a subset of available studies, a random-effects meta-analysis that includes imprecise estimates of treatment effect calculated for all

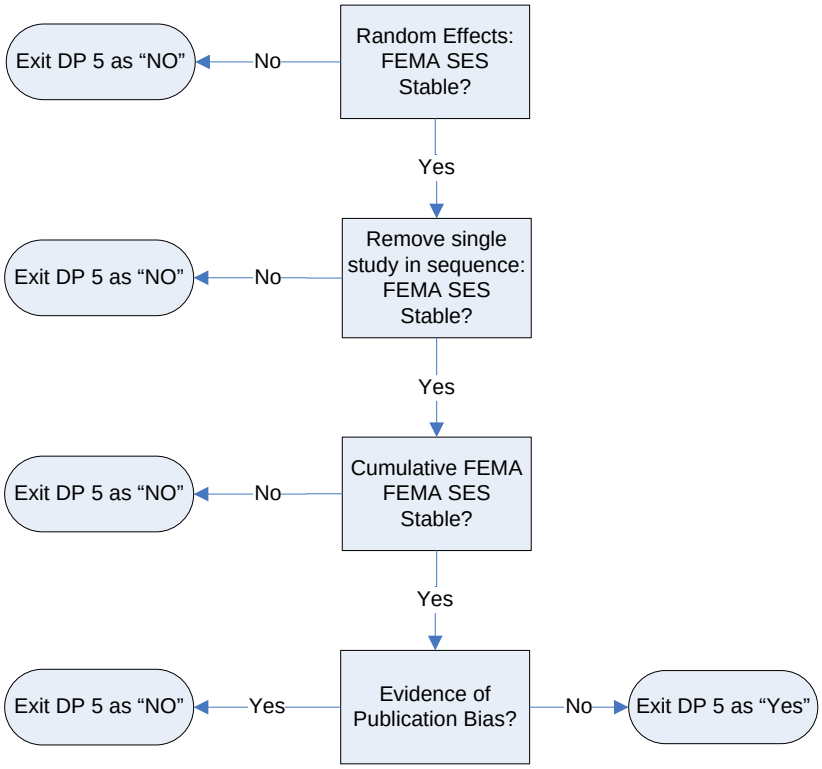
available studies will be performed. For this evidence report, the summary estimate of treatment effect determined by this analysis will be compared to the summary effect size estimate determined by the original fixed-effects meta-analysis. If the random effects effect size estimate differs from the original fixed-effects meta-analysis by >±5%, the original effect size estimate will not be considered stable.

2. *Removal of one study and repeat meta-analysis.* The purpose of this sensitivity analysis is to determine whether a meta-analysis result is driven by a particular trial. For example, a large trial may have a very strong impact on the results of a meta-analysis because of its high weighting.
3. *Publication bias test.* The publication bias test used in this evidence report was that of Duval and Tweedie.(143-146) Based on the degree of asymmetry in a funnel plot constructed from the findings of the included studies, this test(145,146)estimates the number of unpublished studies (and their effect sizes). After addition of any "missing" data to the original meta-analysis, the overall effect size is estimated again. If evidence of publication bias was identified and the summary effect size estimate, adjusted for "missing" studies, differed from the pooled estimate of treatment effect determined by the original fixed-effects meta-analysis by >±5%, the we determined that the findings of our original analysis are not robust and the effect size estimate is not stable.
4. *Cumulative fixed-effects meta-analysis.* Cumulative meta-analysis provides a means by which one can evaluate the effect of the size of the evidence base (in terms of the number of individuals enrolled in the included studies and the number of included studies) on the stability of the calculated effect size estimate. For this evidence report, we performed three different cumulative fixed-effects meta-analyses:
    a. Studies were added in order of weight
    b. Studies were added cumulatively to a fixed-effects meta-analysis by date of publication-oldest study first.
    c. Studies were added cumulatively to a fixed-effects meta-analysis by date-newest study first.

    In each instance, the pooled effect size estimate was considered unstable if any of the last three studies to be added resulted in a change in the cumulative summary effect size estimate effect of >±5%.

Because it is possible to reach Decision Point 6 with two different types of evidence base (100% or <100% ≥75% of total available evidence base), two slightly different sets of sensitivity analyses are needed. Figure E-2 shows the procedural algorithm that was used when dealing with these two types of evidence base.

Figure E-2. Sensitivity Analysis Algorithm 1: Used when Original Fixed-Effects Meta-Analysis Utilized Data from All Available Studies



Decision Points 6 and 7: Exploration of Heterogeneity

We will always attempt to determine the source of heterogeneity when the evidence base consists of 10 or more studies using meta-regression. In preparing this evidence report we did not encounter any situations where we had a heterogeneous evidence base consisting of at least 10 studies. Consequently, Decision Points 6 and 7 are irrelevant to the present report and we do not discuss them further.

Decision Point 8: Are Qualitative Findings Robust?

Decision Point 8 allows one to determine whether the qualitative findings of two or more studies can be overturned by sensitivity analysis. For this evidence report, a single sensitivity analysis was performed–a random-effects cumulative meta-analysis (cREMA). We considered our qualitative findings to be overturned only when the findings of the cREMA altered our qualitative conclusion (i.e., a statistically significant finding became non-significant as studies were added to the evidence base). If the qualitative findings of the last three study additions were in agreement then we concluded that our qualitative findings were robust.

Decision Point 9: Are Data Qualitatively Consistent?

The purpose of this decision point is to determine whether the qualitative findings of an evidence base consisting of only two studies are the same. For example one might ask, "When compared to insulin injection, do all included studies find that inhaled insulin is a significant risk factor for a motor vehicle crash?"

Decision Point 10: Is Magnitude of Treatment Effect Large?

When considering the strength of evidence supporting a qualitative conclusion based on only one or two studies, magnitude of effect becomes very important. The more positive the findings, the more confident one can be that new evidence will not overturn ones qualitative conclusion.

The algorithm divides the magnitude of effect into two categories–large and not large. Determining the threshold above which the observed magnitude of effect can be considered to be "large" cannot usually be determined *a priori*. In cases where it is necessary to make judgments about whether an estimate of treatment effect is extremely large, the project director will present data from the two studies to a committee of three methodologists who will determine whether an effect size estimate is "extremely large" using a modified Delphi technique.

Figure E-3. General Section

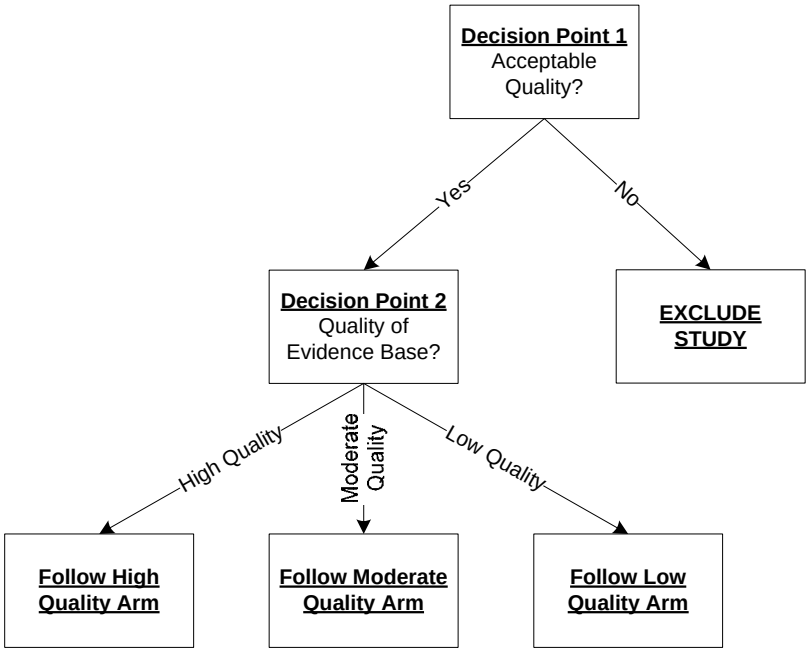


Figure E-4. High Quality Pathway

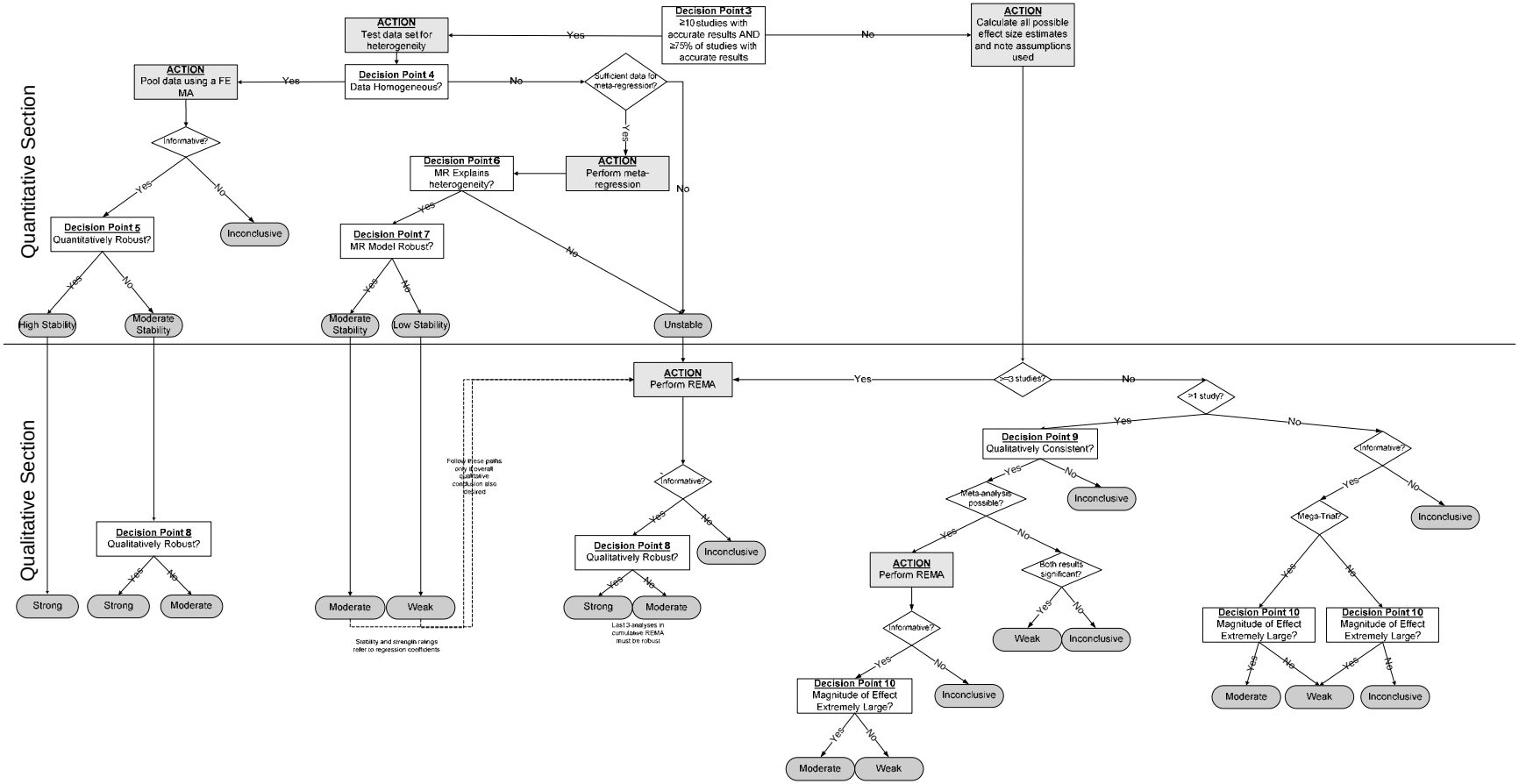


Figure E-5. Moderate Quality Pathway

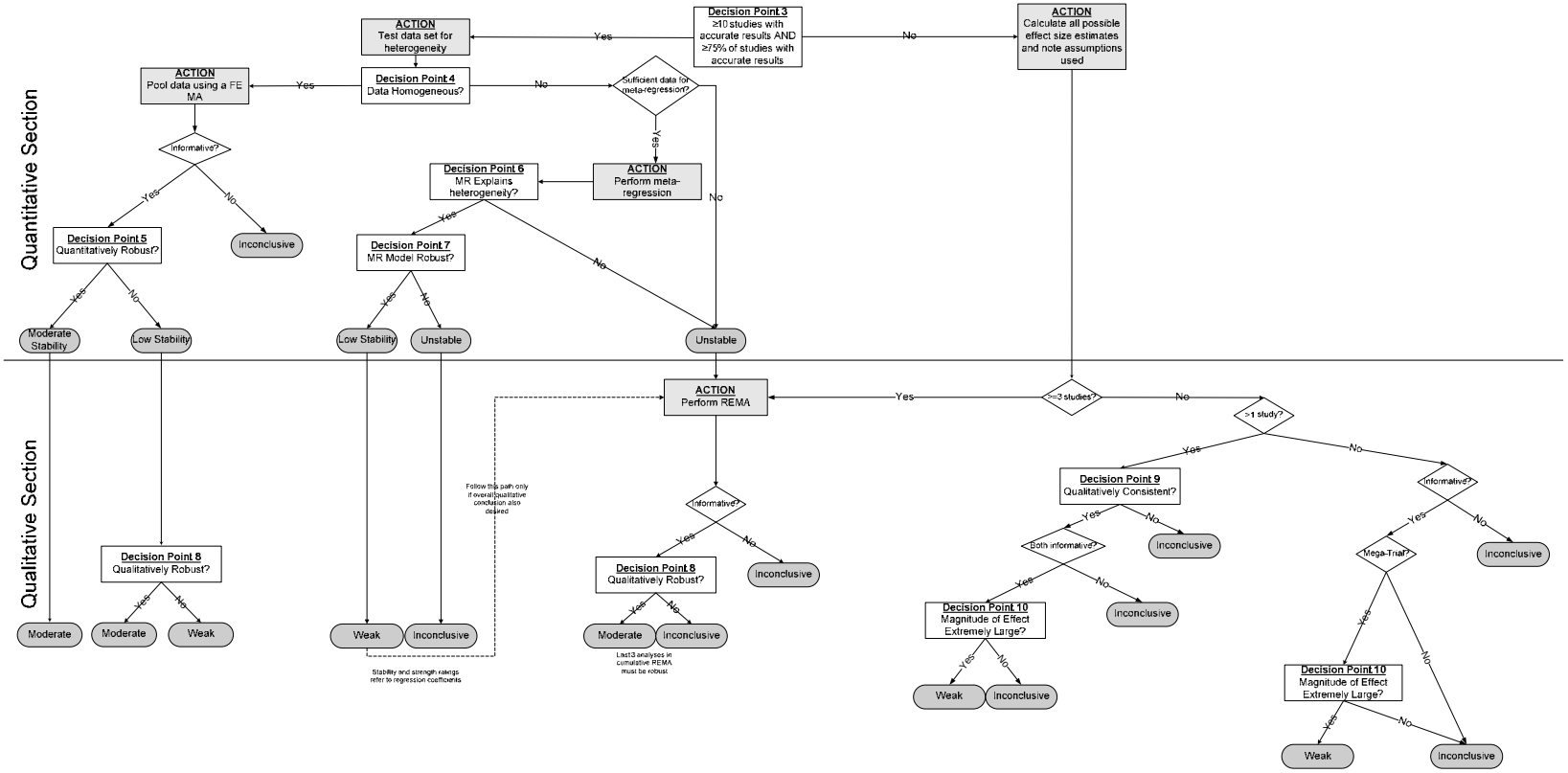
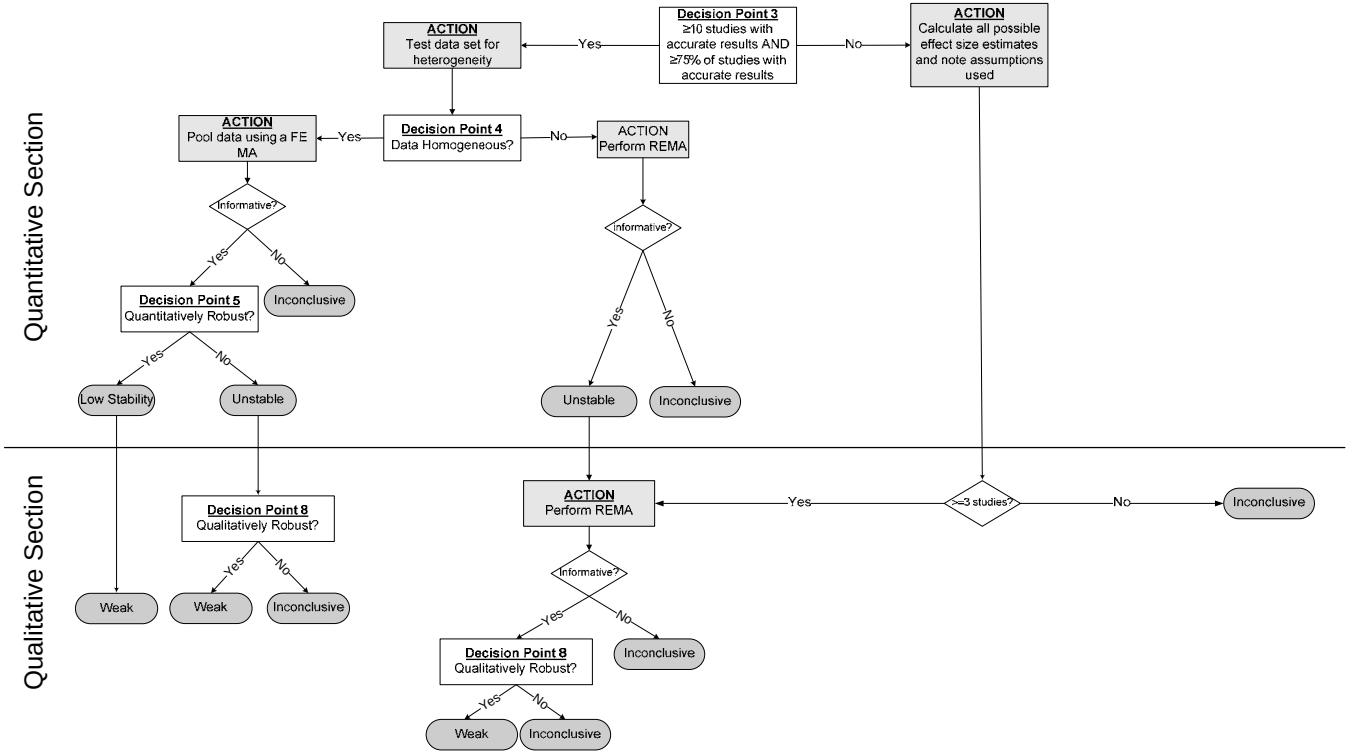


Figure E-6. Low Quality Pathway



Appendix F: Quality Assessment Instruments Used

Three different assessment instruments were used to assess the quality of the studies included in the evidence bases for the key questions addressed in this evidence report; ECRI Quality Scale I for comparative trials, ECRI Quality Scale I for comparative crossover trials, ECRI Quality Checklist III for before-after studies, and a revised version of the Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies.(141)

ECRI Quality Scale I: Controlled Trials (Parallel Arm)

Domain	Question #	Question
Comparability	1	Were patients randomly assigned to the study's groups?
	2	Did the study employ stochastic randomization?
	3	Were any methods other than randomization used to make the patients in the study's groups comparable?
	4	Were patients assigned to groups based on factors other than patient or physician preference?
	5	Were the *characteristics* of patients in the different study groups comparable at the time they were assigned to groups?
	6	Did patients in the different study groups have similar levels of performance on ALL of the outcome variables at the time they were assigned to groups?
	7	Was the comparison of interest prospectively planned
	8	Did ≥85% of the patients complete the study?
	9	Was there a ≤15% difference in completion rates in the study's groups?
	10	Were all of the study's groups concurrently treated?
	11	Was compliance with treatment ≥85% in both of the study's groups?
	12	Were all of the study's groups treated at the same center?
Blinding	13	Were subjects blinded to the treatment they received?
	14	Did the authors perform any tests after completing the study to ensure that the integrity of the blinding of patients was maintained throughout the study?
	15	Was the treating physician blinded to the groups to which the patients were assigned?
	16	Were those who assessed the patient's outcomes blinded to the group to which the patients were assigned?
	17	Was there concealment of allocation?
Outcomes	18	Was the outcome measure of interest objective **and** was it objectively measured?
	19	Were the same laboratory tests, clinical findings, psychological instruments, etc. used to measure the outcomes in all of the study's groups?
	20	Was the instrument used to measure the outcome standard?
Intervention	21	Was the same treatment given to all patients enrolled in the experimental group?
	22	Was the same treatment given to all patients enrolled in the control group
	23	Were the follow-up times in all of the study's relevant groups approximately equal?
Investigator Bias	24	Was the funding for this study derived from a source that does not have a financial interest in its results?
	25	Were the author's conclusions, as stated in the abstract **or** the article's discussion section supported by the data presented in the articles results section?

ECRI Quality Scale II: Controlled Trials (Cross-over Trials)

Domain	Question #	Question
Comparability	1	Were patients randomly assigned to the study's groups?
	2	Did the study employ stochastic randomization?
	3	Were any methods other than randomization used to make the patients in the study's groups comparable?
	4	Were patients assigned to groups based on factors other than patient or physician preference?
	5	Were the *characteristics* of patients in the different study groups comparable at the time they were assigned to groups?
	6	Did patients in the different study groups have similar levels of performance on ALL of the outcome variables at the time they were assigned to groups?
	7	Was the comparison of interest prospectively planned
	8	Did ≥85% of the patients complete the study?
	9	Was there a ≤15% difference in completion rates in the study's groups?
	10	Were all of the study's groups concurrently treated?
	11	Was compliance with treatment ≥85% in both of the study's groups?
	12	Were all of the study's groups treated at the same center?
Blinding	13	Were subjects blinded to the treatment they received?
	14	Did the authors perform any tests after completing the study to ensure that the integrity of the blinding of patients was maintained throughout the study?
	15	Was the treating physician blinded to the groups to which the patients were assigned?
	16	Were those who assessed the patient's outcomes blinded to the group to which the patients were assigned?
	17	Was there concealment of allocation?
Outcomes	18	Was the outcome measure of interest objective **and** was it objectively measured?
	19	Were the same laboratory tests, clinical findings, psychological instruments, etc. used to measure the outcomes in all of the study's groups?
	20	Was the instrument used to measure the outcome standard?
Intervention	21	Was the same treatment given to all patients enrolled in the experimental group?
	22	Was the same treatment given to all patients enrolled in the control group
	23	Were the follow-up times in all of the study's relevant groups approximately equal?
Investigator Bias	24	Was the funding for this study derived from a source that does not have a financial interest in its results?
	25	Were the author's conclusions, as stated in the abstract **or** the article's discussion section supported by the data presented in the articles results section?
Crossover study-specific questions	26	Was there evidence that the results of the experimental groups (in period 1 and 2) did not differ?
	27	Was there evidence that the results of the two control groups (in period 1 and 2) did not differ?
	28	Did ≥85% of patients cross over to the alternative treatment at the intended time?

ECRI Quality Scale III: Pre-Post Studies

Domain	Item	Question
	1	Was the study prospective?
	2	Did the study enroll all patients or consecutive patients?
	3	Were the criteria for including and excluding patients based on objective laboratory and/or clinical findings?
	4	Were the patient inclusion/ exclusion criteria established a priori?
	5	Was the same initial treatment given to all patients enrolled?
	6	Did all patients receive the same subsequent treatment(s)?
	7	Was the outcome measure objective and was it objectively measured?
	8	Did ≥85% of patients complete the study?
	9	Were the characteristics of those who did and did not complete the study compared, and were these characteristics similar?
Investigator Bias	10	Was the funding for this study derived from a source that does not have a financial interest in its results?
	11	Were the author's conclusions, as stated in the abstract or the article's discussion section supported by the data presented in the article's results section?

Revised Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies

The original Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies consisted of ten questions. We adapted the instrument to better capture some sources of bias that were not considered in the original 10-item scale.

Domain	Question #	Question
Selection	1	Do the cases have independent validation?
	2	Are the cases representative?
	3	Are the controls derived from the community?
	4	At the designated endpoint of the study, do the controls have the outcome of interest?
Comparability	5	Does the study control for the most important confounder?
	6	Does the study control for any additional confounders?
Exposure/Outcome	7	Was exposure/outcome ascertained through a secure record (surgical, etc.)
	8	Was the investigator who assessed exposure/outcome blinded to group patient assignment?
	9	Was the same method of exposure/outcome ascertainment used for both groups?
	10	Was the non-response rate of both groups the same?
	11	Was the investigation time of the study the same for both groups?
Investigator Bias	12	Was the funding free of financial interest?
	13	Were the conclusions supported by the data?

Appendix G: Study Summary Tables

Study Summary Tables (Key Question 1)

No studies met the inclusion criteria for this key question.

Study Summary Tables (Key Question 2)

Barkley RA, Murphy KR, O'Connell T, Connor DF. Effects of two doses of methylphenidate on simulator driving performance in adults with attention deficit hyperactivity disorder. J Safety Res 2005; 36(2):121-31.

Key Questions Addressed	1	2	3	4	5	6	7	8	9
		X							

Research Question	To evaluate the effects of two single, acute doses of methylphenidate on the driving performance of adults with ADHD		
Drug examined	Stimulant – methylphenidate (MPH-Ritalin®) : 10 and 20 mg - oral		
Study Design	Randomized double-blind, drug placebo, within-subjects crossover design. All participants were tested at baseline and then experienced all three drug conditions. The drug conditions were: Placebo (P), a single low dose (L) 10 mg MPH-Ritalin®, a single higher dose (H) 20mg MPH-Ritalin ®. Participants were randomly assigned to the 6 orders of drug and placebo conditions: (1) PLH = 7; (2) HPL = 10; (3) LHP = 9; (4) PHL = 8; (5) HLP = 9; (6) LPH = 9.		
Population	**Inclusion Criteria**	Age=18 to 65 yrs. Composite IQ greater than 80 on the Shipley Institute of Living Test. Corrected or uncorrected visual acuity of no worse than 20/30 based on a brief screening using Snelling chart. Valid state driver's license. No evidence of deafness, blindness, severe language delay, cerebral palsy, epilepsy, autism, or psychosis as established through clinical diagnosis interview and medical history. (46% of participants used some form of corrective vision device: glasses, contact lenses…). Patients were required to have received an expert clinical diagnosis of ADHD established not only by meeting the DSM-IV diagnostic criteria but also the judgment of an expert clinician. The following percentage of ADHD subtypes was observed in the sample: 87% combined type, 11% predominantly inattentive type, 0% predominantly hyperactive-impulsive type, and 2% ADHD not otherwise specified. For each testing sessions the participants were instructed not to take any medications 24 hours prior to their testing.
	Exclusion Criteria	Any participants taking antidepressants or other forms pf psychiatric mediation because of the prolonged washout period time such medications typically require before they could be entered in to this protocol. A history of motor or vocal tics or Tourette'S Syndrome (given some controversy over whether stimulants may create or exacerbate these conditions); a history of cardiac surgery; high blood pressure (sustained blood pressure levels above the 95th percentile for age and sex) at baseline ; or cerebral vascular crash ; pregnancy; a history of a previous adverse reactions to stimulants medications; receiving any medications that might adversely affect driving performance; or might be contra-indicated with stimulants; medical conditions that might affect driving performance (i.e., diabetes, retinal disease).
	Study Population Characteristics	n: 52 Age: mean (SD) yrs: 31.3 (SD = 11.3) Sex: % male: 74 Marital status: Married= 26%, never married =67%, divorced or widowed= 7% Ethnic background: White = 83.3%, African-American= 3.7%, Hispanic= 5.6%, Native American= 5.6% and other=1.9% Mean education (years): 14 (SD =2.2) Mean IQ: 104.7(SD=9.7) Mean onset of ADHD symptoms in childhood: 7.1 years (SD=2.6; range= 2-12) Current symptoms of ADHD: 12.5 (SD=3.1) Average number of major life activities impaired: 4.7(SD=1.1) Average number of years of driving experience: 14.5 (SD=11.1) Mean miles driven per week: 252 (SD=203)
	Generalizability to CMV drivers	Unclear
Procedures	For each testing sessions the participants were instructed not to take any medications 24 hours prior to the testing. Participants were randomly assigned to the six orders of drug and placebo conditions. They were required to report to the lab one hour prior to being tested on each of the three testing dates. The medication was then given to the participants to swallow and then the participant remained in the lab for 75 minutes before formal testing began. This was done to insure that the testing started during the peak effects for MPH (60-120 minutes after ingestion). Participants were then tested on the driving simulator (about 15 minutes) after which they were given the continuous performance test.		

<table>
<tr><td>Statistical Methods</td><td colspan="14">All measures were initially analyzed using a one-way (4 drug conditions) multivariate analysis of variance with repeated measures (general linear model, SPSS 11.0). Significance was set at p <0.05. Where Mauchly's Test of Sphericity was significant, the results for the Huynh-Feldt test are reported. Otherwise, the results for Wilk's Lambda are reported. I the omnibus F-test was significant; comparisons were conducted using t- tests for paired samples.</td></tr>
<tr><td rowspan="6">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>NR</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">8.8</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td></tr>
<tr><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>NR</td></tr>
<tr><td rowspan="2">High Quality</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>NR</td><td>Y</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">1. Examiner rating of simulator performance(FAAC virtual reality driving simulator)
2. Self-ratings of simulator performance
The stimulator measures used here were: average speed, the standard deviation of driving speed, the number of collisions, then number of times the turn signal was activated, variation in steering (deviation from right side roadway edge in inches), and time taken to drive the course.
3. Continuous performance test (CPT) to evaluate attention and inhibition. The dependent measures employed here were the total number of omissions (missed targets) and reaction time (RT) variability as measures of inattention, and total commissions (false hits) and RT as measures of impulsiveness.</td></tr>
<tr><td>Results Q2</td><td colspan="14"><u>Continuous performance test results</u>: Only the omnibus F-test for commission errors was significant. Pair-wise comparisons indicates that all three drug conditions (placebo, low dose, and high dose) were significantly improved (fewer errors) compared to the baseline evaluation , suggesting a possible practice effects on this measure.
<u>Simulator driving behavior ratings</u>: On both self ratings and observer ratings, the omnibus-F-tests were significant. Pair- wise comparisons revealed the same pattern of findings for both measures: all three drug conditions were significantly improved over baseline but there were no differences between the drug and placebo conditions.
<u>Simulator scores-standard courses</u>: Significant omnibus tests were found for the number of crashes, steering variability, course driving time, and the number of turn signals activated. Pair –wise comparison for the crash scores revealed that all three drug conditions resulted in significantly lower crash occurrences than in baseline but there were no differences between the drug and placebo conditions. For steering variability, these comparisons showed that variability was significantly greater during the placebo than the baseline condition. However, such variability was significantly lower during the high dose of MPH than during the placebo condition. Course driving time was found to be significantly shorter during all three drug conditions relative to baseline but with no differences between the placebo and drug conditions. For the turn signal score, again all three drug conditions resulted in significantly greater use of the turn signal indicator than in the baseline condition. In this case, however, the low –dose of MPH resulted in significantly greater turn signal usage than in the placebo condition. None of the other pair-wise comparisons for this score were significant.
<u>Stimulator scores-obstacles course</u>: The data for 44 participants were available for analysis for this course. The data for the remaining 10 participants was lot due to simulator malfunctioning or simulator sickness arising by this point in testing such that a few participants could not complete the course.
The steering variability score for one subject during the low dose condition was extreme, resulting in a non-normal distribution. It was normalized when the mean score for this drug condition was substituted for this participant's score. The same problem occurred for a different participant in the high dose condition and was dealt with the same way. The omnibus test for average driving speed during this course was significant. Pair-wise comparisons indicated that speed during the low-dose MPH condition was significantly greater than at baseline, and speed during the placebo condition was marginally greater than at baseline (P = 0.074).
Also average speed during the high dose MPH condition was significantly slower than the low dose MPH condition, and marginally significantly slower than the placebo condition (P = 0.069).
<u>Simulator sickness ratings</u>: Both omnibus test for the self and observer ratings of simulator sickness were significant. Yet pair-wise comparisons showed an opposite patterns of findings. Participants rated themselves as significantly less affected by simulator sickness during all three drug conditions relative to the baseline condition. Observers, however, rated the participants as demonstrating significantly more signs of simulator sickness during all three drug conditions relative to baseline. Again, there were no differences among the three drug conditions in this regard.

<u>Summary:</u> A significant beneficial effect for the high dose of medication was observed on impulsiveness on CPT, variability of steering in the standard driving course, and driving speed during the obstacle course. A beneficial effect of the low dose of medication also was evident on turns signal use during the standard driving course. An apparent practice effect was noted on some of the simulator measures between the baseline and subsequent testing session that may have interacted with and thereby obscured drug effects on those measures. (See Error! Not a valid result for table.)</td></tr>
<tr><td>Authors' Comments</td><td colspan="14">The results, when placed in the context of prior studies of stimulants on driving performance, continue to recommend their clinical use as one mean of reducing the driving risks in ADHD teens and adults.
<u>Impact on industry</u>: Given the significant higher risk of adverse driving outcomes associated with ADHD, industry needs to better screen for ADHD among employees who drive as part of employment so as to improve safety and reduce costs. Use of stimulants to treat the adult ADHD driver may reduce safety risks.</td></tr>
</table>

Table G-1. Means, standard deviations, and statistical test results for the CPT scores and the driving measures for baseline, placebo, low dose (10mg) and high dose (20mg) methylphenidate conditions.

Drug Condition:		1-Baseline		2-Placebo		3-Low Dose		4-High Dose		F	p	Pair-wise Contrasts
Measures	n=	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
CPT Results	52											
Commission Errors		13.3	6.9	8.5	6.8	7.5	7.1	7.2	6.5	34.1	<.001	1 >2,3,4; 2 >4
Omission Errors		4.2	7.1	2.8	6.9	3.2	6.6	2.0	4.3	2.69	NS	–
Reaction Time (1/100 sec.)		377. 8	77.2	388.4	84.0	383.1	78.4	379.9	81.0	1.02	NS	–
Reaction Time Variability		10.4	7.1	9.1	6.5	9.5	9.1	9.3	7.3	0.55	NS	–
Standard Course Results:	52											
Simulator Self-Rating		55.7	8.8	61.4	7.0	60.6	7.5	61.9	7.1	16.5	<.001	1 <2,3,4
Simulator Observer Rating		54.4	5.1	59.2	4.3	60.1	4.4	59.7	4.6	26.90	<.001	1 <2,3,4
Average Speed (mph)		28.8	4.1	29.5	4.2	29.8	4.1	29.8	4.0	1.82	NS	–
Speed Variability (SD)		14.4	2.1	14.7	1.7	14.7	2.2	14.7	1.8	0.05	NS	–
Crashes-Number		1.7	1.4	0.9	1.1	0.9	1.2	0.7	0.9	8.58	<.001	1 >2,3,4
Steering Variability		50.5	16.0	59.5	24.3	55.7	19.4	51.5	11.6	3.13	.031	1 <2; 2 >4
Course Driving Time (sec.)		606.6	81.5	577.5	79.1	572.0	73.7	572.5	77.2	6.16	.001	1 >2,3,4
Number of Turn Signals		15.7	3.8	17.4	4.0	18.2	3.8	17.6	3.9	6.45	.001	1 <2,3,4; 2 <3
Obstacle Course Results:	44											
Average Speed (mph)		38.7	10.1	42.5	10.5	42.6	10.5	39.5	10.6	4.21	.011	1 <3; 3 >4
Speed Variability (SD)		14.7	5.9	14.8	5.6	15.8	6.1	16.7	6.7	2.20	NS	–
Steering Variability		41.5	7.1	37.7	4.9	39.3	13.0	37.4	7.0	2.46	NS	–
Course Driving Time (sec.)		31.8	8.5	29.0	7.7	28.8	7.6	32.0	12.1	2.60	NS	–
Simulator Sickness:	44											
Self-Rating		0.9	1.0	0.5	0.7	0.5	0.7	0.5	0.7	14.10	<.001	1 >2,3,4
Observer Rating		1.0	0.8	0.5	0.6	0.5	0.5	0.6	0.5	13.06	<.001	1 <2,3,4

SD = Standard deviation; F= results for the omnibus F-test; p = probability value for the F-test if significant ($p < 0.05$); Contrasts: Results for pair-wise comparisons among the drug conditions where the omnibus F-test was significant; mph= miles per hours; sec.= seconds

<table>
<tr><td colspan="11">Betts TA, Clayton AB, Mackay GM. Effects of four commonly-used tranquillizers on low-speed driving performance tests. Br Med J 1972 Dec 9; 4(840):580-4.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td></td></tr>
<tr><td></td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="10">To determine whether small repeated doses of commonly used tranquilizing drugs affected performances on low speed vehicle handling tests.</td></tr>
<tr><td>Drug examined</td><td colspan="10">Barbiturates–Amylobarbitone sodium (Amytal sodium) - Five 30mg doses over 36 hours.</td></tr>
<tr><td>Study Design</td><td colspan="10">Randomized, double-blind controlled comparison of four commonly-used tranquilizing drugs (haloperidol, amylobarbitone sodium, chlordiazepoxide, and trifluoperazine) against placebo</td></tr>
<tr><td rowspan="4">Population</td><td colspan="2">Inclusion Criteria</td><td colspan="8">Age =18 to 30 yrs. Volunteers, mainly students. All subjects had to hold full driving licenses. Informed consent was obtained.</td></tr>
<tr><td colspan="2">Exclusion Criteria</td><td colspan="8">Patients suffering from medical or psychiatric conditions that would have invalidated the tests or put the subject at risk from the drugs being studied.</td></tr>
<tr><td colspan="2">Study population characteristics</td><td colspan="8">100 subjects (50 men and 50 women) divided into 5 groups, chlordiazepoxide against placebo, haloperidol against placebo, amylobarbitone sodium against placebo, trifluoperazine against placebo and the double placebo group.
There were 10 men and 10 women in each group
The men had significantly more driving experience (2% level), had driven significantly more miles (1% level), and had significantly more driving convictions (2% level) than the women drivers.
The women scored significantly higher on the N scale of the Eysenck Personality Inventory (2% level).
The mean blood alcohol levels of the subjects on the two test days were very similar, 52.85 mg /100 ml on the first and 52.40mg/ml on the second.
There were no significant differences between the five groups of subjects on any of the above variable.</td></tr>
<tr><td colspan="2">Generalizability to CMV drivers</td><td colspan="8">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="10">Five doses of the drugs were taken in the 36 hours before one of two test periods held on consecutive Sundays; over the 36 hours before the other test period, subject took five doses of the placebo under double-blind conditions. The order of administration of the drug or placebo was randomized to obviate practice effects.
Subjects arrived at the test site on a Wednesday afternoon. They were given the subjective and objective assessment and the first practice session. At the end of the first practice session, they were given two bottles containing the appropriate drugs. The arrived back at the testing centre the following Sunday morning completed the assessments and the driving test.
They were then given a measured dose of alcohol (at the rate of 0-5 gm of alcohol per kg of body weight) to bring their alcohol levels up to about 50mg/100ml. They waited for an hour and then completed the assessments again. They had an alcohol-screening test, which provided an estimate of individual blood alcohol level, and then finally took the driving test again. On the following Wednesday they attended a similar practice session to the first Wednesday, and the following Sunday they completed the same procedure as on the first Sunday.</td></tr>
<tr><td>Statistical Methods</td><td colspan="10">Test I and II: drugs compared with placebo using the split plot analysis of variance.
Test III: For the mean success and mean failure gaps the result were analyzed using the technique of analysis of variance with subgroup of differing sizes.
Objective and subjective assessment results: Comparison of scores was made by using the Wilcoxon matched-pairs signed-ranks test.
All significance levels are at least at the 5% level.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Internal Validity Score: 6.67</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Yes</td><td>NR</td><td>Yes</td><td>Yes</td><td>Yes</td><td>No*</td><td>Yes</td><td>NR</td><td>NR</td><td>Yes</td><td>NR</td><td>Yes</td><td>Yes</td></tr>
<tr><td rowspan="2">Moderate Quality</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td>NR</td><td>Yes</td><td>Yes</td><td>NR*</td><td>No*</td><td>Yes</td><td>Yes</td><td>No*</td><td>Yes</td><td>Yes</td><td>NR</td><td>Yes</td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="10">1. Three Vehicle handling tests: 1, a weaving test; 2, a parking test; 3, a gap estimation test.
- Test I: Weaving test: measurements were made of the time taken to complete the test (forward, reverse, and total time) and the number of bollards hit.
- Test II: Parking test: measured final distance from the kerb, and the number of hits on parked vehicles or on the kerb.
- Test III: Gap estimation test: The mean success gap: the mean of all the chosen gaps through which the subject drove successfully without hitting the bollards; and the mean failure gap: the mean of all the chosen gaps through which the subjects drove and hit one or both of the bollards.
2. Visual screening test, Eysenck Personality Inventory
3.Subjective feeling questionnaire which asked them to rate themselves on a five-point scale against the following parameters: tired, sleepy, restless, Irritable, apprehensive, able to concentrate, found it easy to control you movements, found your hands shaking…
4.Objective Assessment Scale: Subject were rated on the objective presentation of mood, anxiety, and general liveliness on a five-point scale They were also rated on a three-point scale in terms of sleepiness, concentrations, tremor of hands, Romberg's test, nystagmus, finger-nose test, and speech.</td></tr>
</table>

Results	**Vehicle handling tests (**Table G-2): Results refer to effects under drug conditions, and all significance levels are at 5% or better. Test I: When the drug groups were compared with placebo (using the split plot analysis of variance) significant differences emerged in terms of time taken to complete the tests. There was no interaction with alcohol, and the drugs did not affect accuracy on this test. Test II: Comparison between drug and placebo groups (using split plot analysis of variance) showed only one significant difference. One such result could have occurred by chance, and suggest that either the skills needed to do this test were not affected by the drugs, or that it was not sensitive enough. There was no interaction with alcohol. Test III: Significant results obtained by comparing drug versus placebo conditions are summarized in **Error! Reference source not found.** **Objective assessment (**Table G-3**)(**Table G-4**):** Amylobarbitone sodium had a significant euphoriant effect. The results of the observer's assessment as to which weekend the subjects had taken the active drug are shown in Table G-4**.** Subjects taking amylobarbitone sodium could be identified better that would be expected by chance. It is interesting, however, that the subjects in the control group could not be identified with even chance expectancy though the observer knew that a control group existed. **Subjective assessment (**Table G-5): None of the drugs produced significant subjective changes. Amylobarbitone sodium with alcohol had a subjective stimulant effect. In no group could subjects identify the weekend in which they took the active drug with better than chance expectancy.
Authors' Comments	The drugs (with the exception of haloperidol) significantly altered driving behavior though they did not seem to interact significantly with alcohol. There is, therefore, a strong possibility that such drugs will similarly alter driving performance in patients taking them for therapeutic purposes. Since, as these experiments also show, those affected may be subjectively unaware of it, and routine clinical screening is not sensitive enough to detect then, physicians should warn patients of the probability that their driving performance will be affected by such drugs, particularly during the first few days that they are taken. The subjects were in a narrow age band. However, as both men and women who covered a wide range of driving experience were used our group was more representative of the general driving population than in most experiments. To have obtained a completely representative sample would have made the experiment far too long.

Table G-2. Significant Vehicle Handling Test Results by Drug Group

Drug Group	Men	Women
Trifluoperazine	Test 1. Reverse time decreased. Total time decreased	Test 1. Forward time increased. Total time increased
Haloperidol	No Significant Effects	Test 3. Mean success gap decreased
Chlordiaxepoxide	Test 1. Reverse time increased. Total time increased	Test 3. Mean success gap decreased
Amylobarbitone Sodium	Test 3. Mean failure gap increased.	Test 2. Distance from kerb decreased Test 3. Mean success gap increased

Table G-3. Summary of Significant Results of Objective Assessment Scale by Drug Group (Men and Women Combined)

Trifluoperazine	Haloperidol	Chlordiaxepoxide	Amylobarbitone Sodium
Without alcohol			
Reduced Tremor	Decreased spirits. Decreased liveliness of facial expression.	No significant objective effects.	Increased spirits. Increased affective contact. Increased liveliness of facial expression.
With alcohol			
Increased affective contact. Increased speech tempo. Increased liveliness of facial expression. Increased tremor.	Reduced nystagmus.	Increased Rosenberg's sway.	No significant objective effects.

Table G-4. Results of Objective estimate of When Subject Took Active Drug by Groups (Men and Women Combined)

Group	No. Right	No. Wrong	Total
Control group*	5	15†	20
Haloperidol	10	10	20
Trifluoperazine	7	13	20
Chlordiazepoxide	15†	5	20
Amylobarbitone sodium	16‡	4	20

* To be "right" in the control group the observer had to be unable to decide which weekend the subject had taken an active drug. Unlike the subjects he was aware of the existence of a control group.
† Significant (two-tailed) at 5% level. Binomial test, Walker and Lev (1953).
‡ Significant (two-tailed) at 1% level.

Table G-5. Summary of Significant Results by Subjective Assessment Scale by Drug Group (Men and Women Combined)

Trifluoperazine	Haloperidol	Chlordiaxepoxide	Amylobarbitone Sodium
Without alcohol			
No significant subjective effects.	No significant subjective effects.	No significant subjective effects.	No significant subjective effects.
With alcohol			
Less irritable	More dependent. More tense.	No significant subjective effects.	Less tired. Less sleepy.

Byas-Smith MG, Chapman SL, Reed B, Cotsonis G. The effect of opioids on driving and psychomotor performance in patients with chronic pain. Clin J Pain 2005 Jul-Aug;21(4):345-52.

Key Questions Addressed	1	2	3	4	5	6	7	8	9
		X							

Research Question: To determine the effects of long-term stable opioid use on driving performance in patients with chronic pain.

Drug examined: Opioids – Table G-6 presents the analgesic regimens for each participants of the pain group.
The most frequently used opioid analgesic was oxycodone.

Study Design: Non-randomized controlled trial design: Individuals with chronic pain treated with stable regimens of opioid analgesics (opioid group) and individuals with chronic pain who were not taking opioids (nonopioid group) compared to healthy volunteers (normal group).

Population

Inclusion Criteria: Pain group: Minimum age of 21, absence of any physical impairment that might have an impact on driving ability. Ability to pass a sobriety test on the day of the examination. Valid State driver's license. Automobile insurance. Access to an automobile. Patients were required to have reported chronic persistent daily pain for at least 3 months and no change in medication dosage for at least 1 week prior to testing.
Control group: Normal volunteers were recruited via local advertisement.

Exclusion Criteria: For the 3 patients groups: Use of any benzodiazepine or barbiturate for at least a week prior to testing.

Study population characteristics

	Opioid Group	Nonopioid Group	Normal Group
n	21	11	50
Age: (yrs.)	47.7(10.9)	46.5)(6.9)	42.6(9.1)
Sex: F/M	11 / 10	6/5	27/23
Education (Years)	14(3)	15(2.6)	16.6(3.4)
Time driving / wk (hrs)	15.1(4.3)	14.64(12.9)	15.7(16.5)
Driving experience (yrs.)*	31.3(11.5)	28.9 (5.9)	21.9 (11.8)
Pain intensity † (VAS,0-100)*	45.8 (24)	40(21)	4.9(13.9)
Daily morphine dose equivalent ‡	118(327)	_	_
Alertness (categorical,0-6)	4.9 (0.9)	5(1.2)	4.6(1.7)
Sleepy (categorical, 0-6)	1.2(1.3)	0.8(1.3)	1.2
Hrs sleeping (hrs)*	8.61(3.4)	5.96(1.4)	7.31(2.1)
Nervousness(categorical,0-5)*	2.6(1.6)	0.62(1)	1.13(1.4)

*Significance at the 0.05 level; †The most common location of primary pain complain was the low back, but many patients also had cervical complaints and headaches; ‡The opioid pain patients were further stratified for analysis into low dose (less than 20 mg morphine/day) and high dose (greater than 20 mg morphine/day). The cut off of 20mg/day was an arbitrary threshold based on the collective clinical experience in our clinic; _ Data not available

Generalizability to CMV drivers:

Procedures: A total of 215 patients were sent a recruitment letter via mail. Each patient was then telephoned at home or had face to face discussion of the project during their visit to the pain clinic.

Patients participated in the study on 2 separate days within the same week. With 1 comprising field-testing in their own automobile and the other consisting of office-based testing. The field driving test included 2 components presented in random order (coin toss): a community drive and obstacle course testing. Each patient repeated the obstacle course 4 times; an average was computed across all 4 runs of the 5 stations.

Each patient was screened for signs of intoxication prior to beginning field driving test.

Statistical Methods: Each patient repeated the obstacle course 4 times; an average was computed across all runs at each of the 5 stations for the relevant outcome variables. One-way analysis of variance (ANOVA) was used to test for significant differences between the 3 patients groups (opioid, nonopioid and normal) on outcome variables derived from the community drive, the obstacle course, TOVA, and DSST and on baseline characteristics such as age, years of education, years of driving, etc.

Tukey pairwise comparisons were used at the 0.05 level. Analyses of covariance, controlling for age and years of education, was conducted, because patients in the pain groups tended to be somewhat older and less educated than controls. Results from the analyses did not differ from the one-way ANOVAs.

Pearson or point biserial correlations were used to examine the relationship between the patient characteristics and the outcome variables.

Sample size: Originally, study was designed to have 50 patients in each of the 3 groups. This sample size would have 95% power to detect an effect size of 0.80 using a 2-group *t* test with a 0.025 two-sided significance level. In addition, this sample size would have had 95% power to detect, at the 0.05 level, an effect size of 0.106 using a one-way ANOVA. Therefore, in the event that the null hypothesis of no difference between the groups was not rejected, the probability that a real effect of at least the specified effect size was missed is 5%. The study was designed to have high power in the event that the null hypothesis was not rejected. Due to various reasons, 50 people were not enrolled into each of the 3 groups. Hence, Investigators have less than the specified power to detect the effect size for which the study was originally designed. With the current sample size for each of the 3 groups, a one-way ANOVA will have 75% power to detect at the 0.050 level an effect size of 0.106. In addition, the power to detect an effect size of 0.80 using a 2-

<table>
<tr><td></td><td colspan="14">group t test with a 0.025 two-sided significance level is also around 75%. With the current sample size, there is 95% power to detect an effect size of 1, using a 2-sample t test with a 0.025 two-sided significance level. This means Investigators can be fairly certain that when Investigators fail to reject the null hypothesis of no difference that there is no difference of at least 1 standard deviation between the 2 groups.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>No*</td><td>No*</td><td>NR</td><td>Yes</td><td>No*</td><td>NR</td><td>Yes</td><td>NR</td><td>NR</td><td>No*</td><td>NR</td><td>NR</td><td>No*</td></tr>
<tr><td rowspan="2">4.0
Low Quality</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td>No*</td><td>No*</td><td>Yes</td><td>NR</td><td>Yes</td><td>Yes</td><td>Yes</td><td>No*</td><td>No*</td><td>NR</td><td>Yes</td><td>Yes</td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14"><u>1. Field driving tests</u>
Community drive: Patients were evaluated for errors while driving their own automobile trough a predetermined route in the community (7 miles of urban residential driving and 4 miles of interstate driving). Each patient's car was trailed by another car, which contained a camera focused on the rear of the patient's car so that the road and the car could be visualized. The recorded videotape was reviewed at a later date for driving errors by one of the investigators, which included speeding, turning, stopping, and lane violations.
Obstacle Course: Patients were evaluated for speed and accuracy on repeated trials through a 5-station obstacle course that evaluated forward and reverse driving, turning, and parallel parking. Outcome measures: total number of errors- reflected in number of cones struck or run over- and total time to complete the course on all runs)
<u>2. Office-based testing</u>
Test of Variables of Attention (TOVA): Provides a standardized computerized measure of variables important for driving safety, including attention, impulse control and reaction time. The following were automatically recorded: mean reaction time and total errors of commission and omission.
Comparison of these measures during the first and second half of testing provides information to possible patients fatigue effects.
Digit Symbol Substitution Test (DSST) (Subset of the Wechsler Adult Intelligence Scale). Measure of the speed of processing visual information and translating it into motor activity. The number completed correctly in 90 seconds represents the score.</td></tr>
<tr><td>Results Q2</td><td colspan="14">Patient demographics (Table G-6): The patients group tended to have slightly longer driving experience than normal controls (P <0.05). The opioid group reportedly slept longer the night before testing and was significantly more nervous before driving (P <0.05). As expected the mean pain level was significantly higher among the pain groups than the normal volunteers (P <0.05), but there was no difference between the opioid and nonopioid groups.
Community drive: There were no driving errors besides speeding for any patients recorded from the community drive. Greater than 95% of patients in all groups exceeded the speed limit by at least 5 miles per hour, but none greater than 15 miles per hour, and there were no significant differences among groups on speeding.
Obstacle course (Table G-7): No significant group mean differences were found for total time or number of cones impacted or knocked down/run over for any of the 5 stations. In addition, accuracy of parking was not significantly different among the groups. Patients in all groups showed significantly faster times and fewer errors on all courses on the fourth run in comparison to the first run, indicating learning across trial.
To evaluate the effects of different dose levels of opioids, patients in the opioid group were divided into 2 subgroups, comprised of 16 patients taking more than 20 mg of morphine equivalent per day and taking less than or equal to 20 mg per day. When patients in these 2 subgroups were compared, only 1 analysis revealed a significant difference. This difference was on the time to complete the circle course, with a significant faster time to completion in the higher dose group (P <0.05)
TOVA and DSST (Table G-8): There were no statistically significant differences among the groups on any of the TOVA variables. On the DSST, normal patients showed a significant higher score than did either patient group, with no significant difference between the opioid and nonopioid groups of patients.
Relationship between patient variables and major outcome measures (Table G-9): Females, younger patients, and those with more education and lower scores on pain level and on sleepiness performed significantly better on DSST. Because patients in the pain groups tended to be somewhat older and less educated than controls, an analysis of covariance was conducted on DSST scores, controlling for age and years of education. This analysis revealed no significant group differences once these variables were controlled for.</td></tr>
<tr><td>Authors' Comments</td><td colspan="14">The results of this study provide direst evidence that a subset of patients with chronic pain on a stable opioid analgesic regimen is capable of operating a motor vehicle safely during clement weather conditions. The design of this study cannot rule out the possibility that a significant percentage of opioid-treated patients have impaired psychomotor performance that would increase the likelihood of traffic accidents and injuries.
Our results provide empirical evidence that many patients who drive while taking opioid medications have no measurable impairment and are proficient drivers in comparison to normal patients. Any absolute prohibition against driving while taking opioid medications for pain control is contradicted by these results.
<u>Limitations of study:</u>
- The main limitation of this study was the convenience sampling approach taken to acquire patients. Consequently, there was a selection bias, and therefore inference derived from these data cannot and should not be extrapolated to the general population of patients managed with opioids.
- Patients were aware of being evaluated and may have been particularly careful to attend and to perform at their best, when their usual driving performance is less than acceptable.
- This study did not address the situation of long –distance driving over the course of many hours and its results cannot be generalized to extreme rush hour driving or driving conditions in severe weather because it was conducted during clement weather and on weekend day.</td></tr>
</table>

	- Most patients Investigators approached declined participation. The main reason given was inconvenience. It cannot be ruled out that some of these patients were uncertain of their driving skill, perhaps in association with opioid use. - The power of this study would have been greater if more patients had agreed to participate. This limitation had his greater impact on the comparison between opioid versus nonopioid patient groups. Nonetheless, based upon a priori estimate, 20 patients in each group provided adequate statistical power to show significant differences at the 0.05 level. Therefore the probability of yielding a type II error with the comparisons between opioid-treated patients and normal patients is unlikely.

Table G-6. Individual Patient Analgesic Regimens

Patient No.	Analgesic Drug	Dose	Interval
#0001	Hydromorphine	40 mg	Every 4–6 hrs
	Methadone	20 mg	Every 12 hrs
	Venlafaxine	50 mg	Every 8 hrs
	Naproxen	550 mg	Every 12 hrs
#0002	Morphine SR	30 mg	Every 12 hrs
	Rofecoxib	25 mg	Every 12 hrs
	Pamelor	250 mg	Every 12 hrs
#0003	Methadone	15 mg	Every hs
	Oxycodone	5–10 mg	Every 3–4 hrs
	Acetaminophen	325 mg	Every 4 hrs
	Venlafaxine	65 mg	Every day
	Amitriptyline	300 mg	Everh hs
	Gabapentin	2400 mg	Every day
#0004	Propoxyphene	100–200 mg	Every 4–6 hrs
	Acetaminophen	1300 mg	Every 4–6 hrs
	Paroxetine	30 mg	Every day
	Baclofen	10 mg	Every 8 hrs
	Gabapentin	300 mg	Everh hs
	Dextroamphetamine	5 mg	Every 12 hrs
#0005	Hydrocodone	10 mg	Every od
	Gabapentin	900 mg	Every 8 hrs
	Citalopram	60 mg	Every hs
#0006	Methadone	10 mg	Every 12 hrs
	Oxycodone	20 mg	Every 8 hrs
	Acetaminophen	325 mg	Every 8 hrs
	Paroxetine	10 mg	Every day
	Gabapentin	200 mg	Every 8 hrs
#0007	Oxycodone SR	40 mg	Every 12 hrs
	Hydrocodone	5 mg	Every 6 hrs
	Acetaminophen	500 mg	Every 6 hrs
	Amitriptyline	150 mg	Every hs
	Celcoxib	400 mg	Every 12 hrs
	Carisoprodol	350 mg	Every day
#0008	Oxycodone SR	20 mg	Every 8 hrs
	Celcoxib	200 mg	Every day
	Cariosprodol	350 mg	Every 8 hrs
#0009	Methadone	10 mg	Every 6 hrs
	Oxycodone	5 mg	Every wk
	Acetaminophen	325 mg	Every wk
#0010	Oxycodone SR	20 mg	Every 12 hrs
	Hydromorphine	4 mg	Every 4–6 hrs
#0011	Oxycodone SR	20 mg	Every 8 hrs
	Hydrocodone	5 mg	Every 4–6 hrs
#0012	Methadone	10 mg	Every 12 hrs
	Hydrocodone	10 mg	Every 12 hrs
	Acetaminophen	500 mg	Every 12 hrs
	Tramadol	50 mg	Every 12 hrs
	Gabapentin	300 mg	Every 12 hrs
	Cyclobenzaprine	10 mg	Every 8 hrs
#0013	Codeine	30 mg	Every 12 hrs
	Acetaminophen	300 mg	Every 12 hrs
	Pamelor	75 mg	Every day
	Celecoxib	100 mg	Every 12 hrs
#0014	Oxycodone	10 mg	Every 8 hrs
	Acetaminophen	500 mg	Every 12 hrs
	Phenytoin	300 mg	Every 12 hrs
	Fluoxetine	60 mg	Every day
#0015	Oxycodone SR	20 mg	Every 12 hrs
	Oxycodone	5 mg	Every 6 hrs
	Sertraline	100 mg	Every 12 hrs
#0016	Oxycodone SR	40 mg	Every 8 hrs
	Oxycodone	5 mg	Every 4–6 hrs
	Acetaminophen	325 mg	Every 4–6 hrs
	Gabapentin	300 mg	Every 8 hrs
#0017	Propoxyphene	100 mg	Every 8 hrs
	Hydrocodone	5 mg	Every 12 hrs
	Acetaminophen	1200 mg	Every day
	Pamelor	25 mg	Every 12 hrs
	Cyclobenzaprine	10 mg	Every day
	Celecoxib	200 mg	Every 12 hrs
	Neurontin	600 mg	Every 8 hrs
	Tizanidine	4 mg	Every 12 hrs
#0018	Demerol	100 mg	Every 8 hrs
	Rofecoxib	25 mg	Every day
#0019	Oxycodone SR	20 mg	Every 8 hrs
	Oxycodone	10 mg	Every 6–8 hrs
	Sertraline	150 mg	Every day
	Celecoxib	200 mg	Every 12 hrs
#0020	Tramadol	50 mg	Every 6 hrs
	Trazadone	50 mg	Every day
	Celecoxib	200 mg	Every day
	Gabapentin	300 mg	Every 8 hrs
#0021	Methadone	20 mg	Every 12 hrs
#0022	Methadone	10 mg	Every 12 hrs
#0023	Naproxen	250 mg	Every 12 hrs
#0024	Gabapentin	300 mg	Every 8 hrs
	Mirtazapine	30 mg	Every hs
#0025	No medications	NA	NA
#0026	Celecoxib	100 mg	Every 12 hrs
	Sinequan	100 mg	Every hs
#0027	Celecoxib	100 mg	Every 12 hrs
	Sinequan	10 mg	Every day
#0028	No medications	NA	NA
#0029	Dilunisal	500 mg	Every 12 hrs
#0030	Celecoxib	200 mg	Every 12 hrs
#0031	Mexilitine	150 mg	Every 12 hrs
	Baclofen	20 mg	Every 8 hrs
	Sertraline	50 mg	Every day
#0032	No medications	NA	NA

NA, not applicable.

Table G-7. Mean Time (SD) and Errors on Obstacle Course

Task	Opioid Group	Nonopioid Group	Normal Group
Parallel parking			
Time (sec)	57.6 (30.5)	44.5 (10.7)	57.8 (22.3)
Cone impacts	2.4 (1.6)	1.5 (1.2)	2.1 (1.6)
Cones knocked down	0.6 (1.5)	0.1 (0.2)	0.5 (0.9)
Discrepancy from optimal curb distance			
(front tire)	22.1 (14.7)	28.3 (10.6)	24.4 (13.1)
(rear tire)	25.0 (21.2)	23.8 (10.5)	23.3 (10.5)
Circle drive			
Time (sec)	24.5 (10.3)	25.6 (11.6)	24.1 (8.1)
Cone impacts	5.5 (4.0)	4.8 (3.4)	4.7 (3.0)
Cones knocked down	0.6 (0.6)	0.8 (0.7)	0.6 (0.8)
Barrier drive			
Time (sec)	42.7 (6.7)	41.3 (5.9)	41.5 (5.5)
Reverse drive			
Time (sec)	7.6 (3.9)	7.5 (2.9)	9.4 (7.8)
Cone impacts	2.1 (2.7)	1.7 (1.6)	2.5 (2.7)
Cones knocked down	0.7 (1.3)	0.3 (0.5)	0.9 (1.5)
Forward drive			
Time (sec)	8.3 (1.7)	9.5 (2.5)	9.2 (2.6)
Cone impacts	2.8 (3.0)	3.4 (2.6)	3.2 (2.4)
Cones knocked down	0.6 (0.9)	0.8 (1.2)	0.6 (0.8)

Table G-8. Scores on TOVA and DSST Mean SD

Measurement	Opioid Group	Nonopioid Group	Normal Group
TOVA			
Reaction time (msec) First half of test	389.86 (55.67)	394.58 (77.02)	406.91 (87.42)
Reaction time (msec) Second half of test	358.57 (62.05)	379.58 (77.83)	367.23 (69.38)
Errors of omission First half of testing	0.57 (1.16)	0.08 (0.29)	0.47 (1.46)
Errors of omission Second half of test	0.50 (1.09)	0.25 (0.62)	2.57 (7.73)
Errors of commission First half of test	2.00 (3.55)	1.00 (1.54)	0.79 (1.16)
Errors of commission Second half of test	9.21 (7.78)	6.42 (5.95)	5.32 (5.16)
DSST score*	48.13 (13.65)	49.82 (12.02)	59.66 (10.57)

*The normal group performed better than the patients on the DSST, $P < 0.05$.

Table G-9. Pearson Correlations

	Obstacle Course			TOVA			DSST
	Time	Cones Impacted	Cones Knocked Over	Reaction Time	Errors of Omission	Errors of Commission	Score
Sex*	−0.31†	−0.18	−0.10	0.13	−0.13	−0.07	−0.35†
Age	−0.02	0.05	0.16	0.23	0.01	0.06	−0.53†
Yrs of education	0.28‡	0.07	−0.11	0.06	−0.07	−0.16	0.44†
Yrs driving experience	0.13	−0.03	0.04	0.13	0.04	0.15	−0.52†
Hrs driving per wk	0.19	−0.07	−0.12	0.04	0.14	−0.01	−0.20
VAS pain level	−0.02	0.09	0.09	0.08	−0.10	0.28	−0.52†
Hrs slept	−0.07	−0.08	−0.02	−0.20	−0.04	0.02	−0.14
Rating of sleepiness	0.19	0.36‡	0.09	0.38	0.22	0.18	−0.43‡
Rating of nervousness	0.34†	0.19	0.20	−0.09	0.16	0.47†	−0.19
Rating of alertness	−0.05	−0.10	0.02	−0.06	0.11	0.08	−0.10
Morhine equivalent dose level	0.17	−0.03	−0.05	−0.01	−0.13	−0.26	0.22
Effectiveness of pain meds	0.03	0.02	0.16	−0.07	0.28	0.25	0.32

*For sex, a point biserial correlation was used with a positive correlation indicating a higher score on outcome variable for males.
†$P < 0.01$.
‡$P < 0.05$.

<table>
<tr><td colspan="15">Clark CR, Geffen GM, Geffen LB. Role of monoamine pathways in attention and effort: effects of clonidine and methylphenidate in normal adult humans. Psychopharmacology 1986; 90(1):35-9.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td></tr>
<tr><td></td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="14">To examine the effect on auditory selective attention of methylphenidate and clonidine administered intravenously to normal volunteers.</td></tr>
<tr><td>Drug examined</td><td colspan="14">Stimulant - Methylphenidate hydrochloride (Ritalin ®) - (0.65 mg/kg) IV</td></tr>
<tr><td>Study Design</td><td colspan="14">Randomized, crossover trial in which 10 male volunteers received methylphenidate, clonidine and placebo</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Right handed male volunteers between the ages of 18 and 30 years who were screened for medical and psychiatric abnormalities and for hearing deficits. Consent in writing was obtained.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">NR</td></tr>
<tr><td>Study population characteristics</td><td colspan="13">Ten right handed male volunteers between the ages of 18 and 30 years.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="14">Each subject was informed of the drugs to be used and their possible side effects.
At the beginning of each experimental session 200µg clonidine hydrochloride (Catapres) or 0.65mg/kg methylphenidate hydrochloride (Ritalin® provided in 20 mg dry ampoule) or placebo was administered intravenously. The three administrations were completed in random order over sessions. Drugs and placebo were administered in 10 ml solution over 5 min via an indwelling venous cannula on the dorsum of the hand. Testing started approximately 20 min after drug infusion.
In each of three experimental sessions held at 3-7 days intervals, they completed six lists on the tasks.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">All measures obtained from the two active drugs conditions, including cardiovascular parameters, were compared using repeated measures analysis of variance with the equivalent scores from the placebo condition. Post hoc analyses were conducted where necessary using the Fisher test in order to interpret significant interactions.</td></tr>
<tr><td rowspan="6">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">7.9</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td></tr>
<tr><td>N</td><td>NR</td><td>NR</td><td>NR</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>NR</td></tr>
<tr><td rowspan="2">Moderate</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>NR</td><td>Y</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">1. Dichotic monitoring: Subjects were administered a dichotic monitoring task in which they were required to detect nominated target words and discriminate them from phonemic distractors.
In each of three experimental sessions held at 3-7 days intervals, they completed six lists on the tasks. Two in which they were required to divide their attention equally between ears (divided attention), two in which they were required to focus their attention on the left ear and ignore the right, and two in which they were required to focus their attention on the right ear and ignore the left (focused attention). The ordering of strategies was counterbalanced to limit strategy priming effects.
The dependent measures obtained from the dichotic monitoring tasks were:
A Ipsilateral target detection rate
B. Ipsilateral plus contralateral rate of response to distractors (error rate)
C. Ipsilateral response time to targets and a signal detection measure of target discrimination (target detection rate-error rate)
2. Cardiovascular effects
3. Subjective state</td></tr>
<tr><td>Results</td><td colspan="14">Dichotic monitoring: There was a significant effect of attention strategy during the placebo condition on target detection rate (PP ≤0.001), error rate (PP = 0.039), target discrimination and response time (PP = 0.002). More targets were detected, more errors committed, target discrimination was better and response time was faster during focused than divided attention.
A comparison of methylphenidate and placebo conditions found that methylphenidate affected error rate
(Drug X Attention strategy: PP = 0.012), tended to affect target detection rate (Drug X Attention strategy: PP = 0.065), but had no effect on target discrimination or response time (PP >0.10). Both error and target detection rates were higher following methylphenidate during divided but not focused attention.
Subjective state: Following methylphenidate administration, most subjects became noticeably talkative and a number made comments relating to level of awareness and attention state. One subject indicated that in performing the task he didn't have to concentrate as much as normal to hear the words and that he was much more aware of things. Another commented that he was thinking of too many things. Two subjects felt almost bale to do two things at once. One said that whereas a tendency to daydream normally took his attention off task, he was now able to do both at the same time</td></tr>
</table>

Authors' Comments	Following placebo, performance was better when attention was focused than when divided. *Methylphenidate had no effect on target discrimination or response time but raised the rate of response and had marked effects on spontaneous behavior in which an increased attention capacity was generally reported*. The effects on attention of the pharmacological agents employed in this study are attributed to their effects on central monoamines. The disparity noted between objective and subjective assessments of attention is discussed in terms of voluntary allocation of effort.

<table>
<tr><td colspan="15">Clark CR, Geffen GM, Geffen LB. Role of monoamine pathways in the control of attention: effects of droperidol and methylphenidate in normal adult humans. Psychopharmacology 1986; 90(1):28-34.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td colspan="2">2</td><td colspan="2">3</td><td colspan="2">4</td><td colspan="2">5</td><td colspan="2">6</td><td colspan="2">7</td><td>8</td></tr>
<tr><td></td><td colspan="2">X</td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td>X</td></tr>
<tr><td>Research Question</td><td colspan="14">To examine the effect on auditory selective attention of methylphenidate and droperidol administered intravenously to normal volunteers.</td></tr>
<tr><td>Drug examined</td><td colspan="14">Stimulant - Methylphenidate hydrochloride (Ritalin ®) - (0.65 mg/kg) IV</td></tr>
<tr><td>Study Design</td><td colspan="14">Randomized, crossover trial in which 12 male volunteers received methylphenidate, droperidol and placebo.</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Right handed male volunteers between the ages of 18 and 30 years who were screened for medical and psychiatric abnormalities. Normal hearing range was assessed by pure tone audiometry, with the maximum acceptable hearing loss on each ear being 25 decibels (ISD) between 125 and 4000Hz.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">NR</td></tr>
<tr><td>Study population characteristics</td><td colspan="13">Twelve right handed male volunteers between the ages of 18 and 30 years.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="14">Each subject was informed of the drugs to be used and their possible side effects.
At the beginning of each session either 15 µg / kg droperidol or placebo was administered and this was followed 1 h later by the administration of either 0.65mg/kg methylphenidate or placebo. The delay of 1 h in each session between drug administrations was introduced to allow the antagonist action of droperidol to take full effect.
Methylphenidate hydrochloride (Ritalin®) was provided in 20 mg dry ampoules. Droperidol (Dropleptan®) was provided as 10 mg in 2ml ampoules. Drugs and placebo were administered in 10 ml solution over 5 min via an indwelling intravenous cannula on the dorsum of the hand.
Four drug sequences were employed: 1) placebo followed by placebo (placebo condition), 2) placebo followed by methylphenidate (methylphenidate condition), 3) droperidol followed by placebo (droperidol condition), 4) droperidol followed by methylphenidate (droperidol + methylphenidate condition).
Testing started approximately 20 min after the second injection and lasted approximately 1h.
Subjects Investigators seated in a sound attenuated-room and received their instructions through a two-way intercom. set. The subjects listened to pairs of words and depressed one of two microswitches using the forefinger ipsilateral to the ear in which predesignated target words were detected. Before each list subjects Investigators shown a card containing the relevant target word and distractor word.
Attention conditions (divided or focused) were ordered randomly provided that the divided attention strategy was completed either first or last in order to limit any strategy priming effects.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Divided and focus attention scores from each drug conditions (methylphenidate, droperidol, droperidol + methylphenidate) were compared with those from the placebo conditions using repeated measures analysis of variance. Post hoc analyses were conducted where necessary using the Fisher test in order to interpret significant interactions. Cardiovascular parameters and questionnaire scores from each of the three drug conditions were also compared to placebo using repeated measures analysis of variance.</td></tr>
<tr><td rowspan="6">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">8.8</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td></tr>
<tr><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>NR</td></tr>
<tr><td rowspan="2">High</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>NR</td><td>Y</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">1. Dichotic monitoring: Subjects were administered a dichotic monitoring task in which they were required to detect nominated target words and discriminate them from phonemic distractors. In each of the four test sessions in which drugs were administered, subjects performed one list in which they were required to divide their attention equally between the left and right ear stimuli (divided attention) and two lists in which they were required to focus their attention on either the left or right ear and to ignore the other (focused attention).
The dependent measures obtained from the dichotic monitoring tasks were:
A. Ipsilateral target detection rate
B. Ipsilateral plus contralateral rate of response to distractors (error rate)
C. Ipsilateral response time to targets and a signal detection measure of target discrimination (target detection rate-error rate)
3. Subjective state: Immediately, before testing during each drug session, subjects were asked to complete a questionnaire designed to assess their subjective state on the six dimensions of anxiety, alertness, elation, lethargy, relaxation and depression. (These constructs were drawn from the Brief Psychiatric Rating Scale and the Inpatients Behavioral Rating Scale). The subjective state questionnaires were scored by coding from 1 to 7, with 1 representing the pole “not at all” and 7 representing “extremely so “.</td></tr>
</table>

Results Q2	**Dichotic monitoring**: There was a significant effect of attention strategy during the placebo condition on target detection rate (P = 0.002), target discrimination (P = 0.016) and response time (P = 0.019). More targets were detected, target discrimination was better and response time was faster during focused than divided attention. A comparison of methylphenidate and placebo conditions showed no significant effect or interactions involving drug condition, indicating that methylphenidate had no effect on dichotic monitoring task performance. **Subjective state**: Subjects rated themselves more alert (PP <0.003), more elated (PP = 0.001), less lethargic (PP = 0.008), and less depressed (PP = 0.013) in the methylphenidate than the placebo condition. **Spontaneous behavior**: Within 10 min following methylphenidate administration most subjects became noticeably talkative. Some subjects mentioned that the urge to talk was overwhelming and difficult to restrain. Within 1 h of methylphenidate administration, five subjects made comments relating to perceptual experiences. Some noticed more of their environment: "…I am noticing things which I haven't noticed before in this room…", "…I have seen them before but I didn't realize the details…"; others commented on increased awareness of sounds, brighter colors, more vivid and clear images or a generally increased awareness of things, e.g."…the visual experience is a little bit clearer…". Six subjects referred to increased mental activity. One commented that he was mentally doing three things at once, while others mentioned having more mental imaged than normal, an increase in he quantity of thoughts , thoughts rushing through the head or increased inquisitiveness. Seven subjects indicated that they found it difficult to concentrate on the task and felt they were easily distracted. A number of these commented on an inability to direct their attention or their thought, while others commented on being able to do so but for short burst only before becoming distracted. Others mentioned becoming distracted by irrelevant features of the task or their attention being unintentionally shifted from one irrelevant thing to the next.
Results Q8	Methylphenidate administered 1h after droperidol treatment reversed all signs of withdrawal and depression. On addition, subjects made comments such as "feel relax and alert", "feel good now". "feel terrific now" and "ready for action". Four subjects made comments which indicated than following droperidol certain of the subjective effects of methylphenidate were less intense than when methylphenidate was administered alone. For example three subjects mentioned than although they experienced euphoria and talkativeness as before, it lasted for a considerably shorter period. Only 2 subjects commented on the ability to concentrate: both mentioned being easily distracted, and one mentioned losing his train of thought more often than normal though he could "bring himself back" once this was realized. Only one subject commented on perceptual experiences when methylphenidate had reversed the effects of droperidol: " this (methylphenidate is very much an outlook sensation drug which means you respond to a lot of different things at the same time …I am aware of my scope of vision … trying to take everything in at once".
Authors' Comments	Performance following placebo was superior when attention was on one ear than when divided between the ears. *Administered alone, methylphenidate had no effects on dichotic measures of attention but had marked effects on spontaneous behavior, when most subjects reported a substantial increase in both the field and distractibility of attention.* The disparity between the subjective and objective assessments of the effects of the drug on attention is discussed in terms of the degree of mental effort voluntarily brought to bear by subjects in the selective allocations of their attentional capacity.

<table>
<tr><td colspan="15">Coda BA, Hill HF, Hunt EB, Kerr EB, Jacobson RC, Chapman CR. Cognitive and motor function impairments during continuous opioid infusions. Hum Psychopharmacol 1993; 8:383-400.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td></tr>
<tr><td></td><td>X</td><td></td><td>X</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="14">1) To assess the magnitudes of cognitive and motor effects of morphine and alfentanil at different, steady plasma opioid concentration within the analgesics plasma opioid concentration ranges of the two drugs.
2) To examine the relationships between the magnitude of cognitive and motor effects and plasma concentrations of alfentanil and morphine.
3) To determine whether differences exist in effects of those two mu agonists on cognition or motor function at plasma opioid concentrations considered equally analgesic.</td></tr>
<tr><td>Drug examined</td><td colspan="14">Opioids – Morphine and alfentanil continuous infusion (Opioids infusion via an IVAC volumetric infusion pump that was controlled by a Macintosh computer).</td></tr>
<tr><td>Study Design</td><td colspan="14">Randomized double-blind, crossover in which 15 healthy volunteers received morphine, alfentanil and saline.</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Age = 21 to 37 yrs. Healthy male volunteers Literate, proficient in English, in good health and none had a history of drug abuse. Informed consent.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">NR</td></tr>
<tr><td>Study population characteristics</td><td colspan="13">15 healthy male volunteers. Subject ranged in age from 21 to 37 years. Body weight ranged from 55.4 to 98.6 kg; all were within ±10 per cent of normal weight for height.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="14">Subjects remained seated in a hospital bed inside a sound-attenuated testing chamber throughout each pretest and infusion session. Each subject participated in three pretest sessions on different days; two pharmacokinetic tailoring session involving bolus doses of morphine and alfentanil and one additional session for test battery practice. Each subject participated in three infusion sessions with morphine, alfentanil and saline infused on different days. The order of drug and saline sessions was double-blind and counterbalanced across subjects and a minimum of 7 days separated any two sessions for each subject.(Table G-10)</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Investigators used a MANOVA for repeated measures (two trial factors) for each of the variables, testing alfentanil, morphine and saline at zero, low, medium and high plasma concentrations. Each analysis yielded an effect for Drug, Target concentration and Drug X Target concentration interaction.
Investigators performed post-hoc paired t-test where indicated, to determine whether he effects of morphine and alfentanil differed significantly.
Investigators performed repeated measures analyses of variance (ANOVA) to contrast changes in spectral edge and delta ratios across the three conditions on scores derived from cortical power spectral analyses of the EEG data.
The criterion for statistical significance was alpha = 0.05 in all cases.
In addition to analyzing mean differences, Investigators also evaluated the data set for individual differences in treatment effects.
Investigators performed a series of multiple regressions with the opioid infusion data (corrected for saline infusion results), in which individual subjects were represented as fixed effects (dummy codes). Each regression predicted performance (motor or cognition) on the basis of different combinations of drug, measured plasma alfentanil or morphine concentration, and individual subject differences.</td></tr>
<tr><td rowspan="6">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>NR</td><td>NR</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">8.4</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>NR</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>NR</td><td>Y</td><td>NR</td></tr>
<tr><td rowspan="2">High Quality</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>NR</td><td>Y</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">1. Motor performance:
-Tapping (simple motor performance)
-isometric force: Maintenance of low constant force with and without visual feedback (indicators of complex motor performance)
2. Cognitive performance:
-Rapid Single Visual Presentation (RSVP). This test measures the speed and accuracy of verbal comprehension. The procedure records the time taken to read words in sentences of a standardized text passage as a measure of comprehension time for individual words.
3. Subjective side- effects: Subjects rated alertness, nausea, itching and mood using 100 mm visual analog scales (VAS) at baseline and at each target concentration plateau.
4. EEG and sedation: To evaluate the possibility that the study drugs induced a generalized central nervous system depression.</td></tr>
<tr><td>Results Q2</td><td colspan="14">Motor performance (Table G-11and Table G-13): Morphine and alfentanil did not affect simple motor performance (tapping).
In contrast, accuracy of force maintenance diminished significantly in response to the opioids, most clearly when subjects could not compensate for impairment by using visual feedback. Subject's ability to maintain constant force did not change during saline infusion, but decrease as plasma opioid concentration increased.</td></tr>
</table>

	Subjective side effects: There were no significant differences in side- effect intensities between drugs. Individual differences in treatment effect: Individual differences in cognitive and motor opioid side-effects are very large, even under highly controlled conditions. Clinical studies of such impairment will require large sample sizes and should attempt to account for individual differences by employing block design or correlations techniques. **EEG effects**: Investigators examined the EEG data obtained at the highest plasma concentration to contrast changes in spectral edge and delta ratio across the three drug conditions: alfentanil, morphina and saline. Neither spectral edge (p = 0.421) nor delta ratio (p = 0.252) demonstrated significant differences across the three drug conditions. These outcomes suggested that opioid-related impairment of cognitive and motor function were not due simply to diminished arousal or general central nervous system depression.
Results Q4	Target plasma concentration plateaus for alfentanil: 16, 32,64 ng/ml Target plasma concentration plateaus for morphine: 20, 40,80 ng/ml **Motor performance (Results** Table G-11**and** Table G-13**)**: Error in force maintenance with visual feedback increased from 0.28(SE, 0.02) N at baseline t o 0.57 (SE, 0.06) N at the highest alfentanil concentration (64 ng/ml), and from 0.27 (SE, 0.02) N at baseline to 0.63(SE, 0.11) N at the highest morphine plasma concentration (80ng/ml). Error in force maintenance without visual feedback was greater at baseline than with visual feedback and this error increased further with increased opioid plasma concentrations. Baseline error of 1.02 (SE, 0.06) N rose to a maximum of 1.75 (SE, 0.15) N at the highest alfentanil plasma concentration, and baseline error of 0.99 (SE, 0.07) N increased to 2.07 (SE, 0.21) N at the highest morphine plateau. While the absolute magnitude of the decrease in accuracy of force maintenance was greater at all time points without visual feedback (i.e., a maximum change of 1.0 versus 0.3N), the changes relative to baseline were about the same with and without feedback. The error in force maintenance approximately doubled at the highest opioid plasma concentration plateau with and without visual feedback. A *post-hoc* comparison of effects of morphine and alfentanil on force maintenance at each drug level revealed no significant differences between the two opioids (paired Student's *t* tests, p = 0.813, 0.24, 0.192, 0.332 at baseline, low, medium, and high opioid concentrations respectively). Thus the highly significant Drug x Target concentration effect is due to differences between the opioids and saline(P <0.05) **Cognitive performance (Results** Table G-11**,** Table G-12 **and** Table G-13**):** Both opioids exerted minimal effects on *reading time expressed* as *median word time* at the lower target plasma concentrations. However, group averages for median reading time increased by 28 percent at the highest alfentanil target concentration (64ng/ml) and 33% at the highest morphine plateau (80ng/ml). Investigators found a significant Drug x Target concentration effect for the average median reading time. A *post hoc* comparison *(*Student's *t* test) demonstrated significant difference at the low opioid level only (slower median word time with alfentanil (p = 0.029). This difference failed to reach significance when corrected for multiple comparisons (p = 0.116). The effects of alfentanil and morphine on reading speed did not differ significantly from each other at any other target plasma concentration (Student's *t* tests, p = 0.225, 0.029, 0.776,and 0.534 at baseline, low, median and high targets respectively). Saline infusion had no significant effects on reading time; thus, the significant Drug x Concentration effects is mostly due to differences between the opioids and saline(P <0.05) **Subjective side effects**: The magnitude of each subjective side effect increased with increasing plasma concentrations of morphine and alfentanil
Authors' Comments	Authors stated that their results show that alfentanil and morphine can impair performance on some but not all motor tasks at analgesic plasma concentrations, and that the magnitude of such impairment is related to plasma opioid concentration. The opioids exerted no significant effects on simple motor tasks or the ability to mobilize force, but they impaired performance on more complex tasks. Investigators found that plasma concentration s of morphine and alfentanil which degraded reading speed and force maintenance had little or no influence on immediate recall of textual information or on rate of repetitive motor activity. Morphine and alfentanil demonstrated no significant effects at any of the plasma concentration studied here on the ability to comprehend the standard narrative passages during drug infusion. At these plasma opioid concentrations, subjects increased time spent reading individual words in order to maintain comprehension and accuracy of recall. Authors concluded that: 1) Continuous infusions of morphine and alfentanil impair some key elements of cognition and motor function within the range of plasma opioid concentration s associated with clinical analgesia. 2) The magnitude of effects on sensitive elements of cognition and motor function are related to plasma concentration with each opioid. 3) The impact of these two mu-agonists on ceratin key aspects of cognition and motor function do not differ at equally analgesic plasma opioid concentrations. 4) The therapeutic margins of morphine and alfentanil are nearly identical when cognition and motor effects are considered along with other opioid side-effects such as nausea, sedation, mood alteration and respiratory depression.

Table G-10. Constants and Exponential for Biexponential Equations Describing Concentration

	Alfentanil					Morphine				
Subject	Dose wt	*A*	B	*α*	*β*	Dose wt	*A*	*B*	*α*	*β*
1	936	94·1	43·8	0·373	0·0152	7488	405·8	38·5	0·484	0·0115
2	1098	56·7	54·0	0·384	0·0160	8487	1088·1	36·4	0·488	0·0050
3	1250	70·2	38·0	0·265	0·0109	9996	872·8	44·4	0·530	0·0077
4	1005	56·1	34·1	0·384	0·0170	8040	746·2	42·4	0·738	0·0104
5	1194	50·8	29·9	0·132	0·0057	9552	837·4	36·2	0·558	0·0091
6	1170	73·5	48·8	0·287	0·0113	9360	602·9	57·4	0·645	0·0074
7	1245	65·1	37·4	0·255	0·0121	9960	686·5	30·9	0·455	0·0098
8	989	66·1	38·0	0·256	0·0122	9720	802·1	55·4	0·580	0·0106
9	1274	143·3	35·8	0·285	0·0088	10200	540·3	40·4	0·453	0·0106
10	1050	56·1	34·9	0·228	0·0137	8400	420·5	47·5	0·467	0·0098
11	1044	59·3	37·0	0·144	0·0065	8352	696·2	28·9	0·358	0·0074
12	1018	65·4	42·3	0·333	0·0092	8148	585·3	42·2	0·627	0·0101
13	1118	112·8	64·9	0·224	0·0081	8944	686·4	47·6	0·586	0·0102
14	1233	57·3	23·3	0·167	0·0104	9864	741·0	64·3	0·440	0·0081
15	996	80·0	42·2	0·358	0·0100	7968	606·7	50·2	0·706	0·0058
Mean	1107	73·8	40·3	0·272	0·0111	8845	687·9	44·2	0·541	0·0087
SD	—	24·4	9·7	0·081	0·0032	—	169·9	9·5	0·103	0·0018
SE	—	6·5	2·6	0·022	0·0008	—	45·4	2·5	0·027	0·0005
%CV	—	33·1	23·9	29·9	28·8	—	24·7	21·5	19·0	20·9

A and *B* are extrapolated *y*-axis intercepts from biexponential fits. *α* and *β* are hybrid rate constants for drug distributio and elimination.

Table G-11. Multivariate Analysis of Results for Cognitive and Motor Function Measures

Effect measures	df	*F*	*P*
Motor performance			
Tapping dominant hand:			
Drug	2,13	2·580	0·114
Target concentration	3,12	2·341	0·156
Drug × target concentration	6,9	1·564	0·262
Tapping nondominant hand:			
Drug	2,13	·396	0·681
Target concentration	3,12	1·316	0·315
Drug × target concentration	6,9	1·761	0·214
2-Finger tapping, alternate hands:			
Drug	2,13	·634	0·546
Target concentration	3,12	·854	0·491
Drug × target concentration	6,9	2·709	0·087
Force maintenance with feedback:			
Drug	2,13	5·084	0·023*
Target concentration	3,12	12·092	0·001*
Drug × target concentration	6,9	2·486	0·106
Force maintenance without feedback:			
Drug	2,13	5·399	0·020*
Target concentration	3,12	35·602	0·000*
Drug × target concentration	6,9	12·069	0·001*
Cognitive performance			
Median word reading time:			
Drug	2,13	6·177	0·013*
Target concentration	3,12	2·848	0·082
Drug × target concentration	6,9	6·043	0·009*

*$p < 0.05$

Table G-12. Mean RSVP Proportion Correct (SD)

Target concentration	Saline	Morphine	Alfentanil
Low	0·79 (0·21)	0·82 (0·17)	0·85 (0·22)
Medium	0·80 (0·27)	0·65 (0·22)	0·83 (0·18)
High	0·73 (0·20)	0·77 (0·23)	0·76 (0·19)

Table G-13. Median Word Time and Error in Force Maintainance Without Visual Feedback

Drug	Morphine			Alfentanil		
Target (ng/ml)	20	40	80	16	32	64
Median word time						
Drug plateau	424 (22)	472 (36)	559 (47)	460 (22)	466 (28)	560 (28)
Sham increase	456 (77)	416 (35)	603 (76)	469 (38)	436 (44)	576 (76)
Force maintenance error						
Drug plateau	0·98 (0·08)	1·19 (0·16)	2·07 (0·21)	1·16 (0·14)	1·57 (0·20)	1·75 (0·16)
Sham increase	0·90 (0·12)	1·62 (0·26)	3·05 (0·73)	1·26 (0·23)	1·21 (0·22)	1·41 (0·36)

Values are means (± SE) for 15 subjects at each plateau, and for five subjects at each sham increase. There were no significant differences between plateau values and sham increase values at each level for either drug (Student's *t*-tests).

<table>
<tr><td colspan="15">Ghoneim MM, Mewaldt SP, Thatcher JW. The effect of diazepam and fentanyl on mental, psychomotor and electroencephalographic functions and their rate of recovery. Psychopharmacologia 1975 Oct 14;44(1):61-6.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td></tr>
<tr><td></td><td>X</td><td></td><td></td><td></td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="14">1. To what extend does a single dose of diazepam or fentanyl affect mental and psychomotor functions in man?
2. How fast is the rate of recovery of these functions if they are compromised?</td></tr>
<tr><td>Drug examined</td><td colspan="14">Opioids – Fentanyl (0.1or 0.2mg) Intravenously</td></tr>
<tr><td>Study Design</td><td colspan="14">Randomized, double-blind, crossover trial in which 10 healthy volunteers received diazepam, fentanyl and placebo.</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Age = 21 to 25 yrs. Healthy male volunteers. Informed consent.
Subjects were instructed to abstain from any stimulant or depressant beverages from 5p.m. on the day preceding the study.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">NR</td></tr>
<tr><td>Study population characteristics</td><td colspan="13">Ten healthy male volunteers aged 21 to 25 years (mean 22.9 years ±1.5 SD)</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13"></td></tr>
<tr><td>Procedures</td><td colspan="14">Before the start of the actual experiment, each volunteers attended two sessions for pretraining on the psychological tests in order to diminish the effects of learning. Upon arrival at the laboratory an electroencephalogram (EEG) was taken and a battery of psychological tests was administered. These constituted our base line for the subjects following which the injections were given. The treatment consisted of diazepam (Valium) 10 and 20 mg, fentanyl (Sublimaze) 0.1 and 0.2 mg and placebo (Saline) given intravenously at weekly interval. They were assigned to a Latin Square design and administered under double-blind conditions. Post injections, all the tests and EEG were repeated after 2, 6, and 8hrs. The subjective rating was also administered 0.5 hr after injection.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">The results were analyzed by means of a 4x5 analysis of variance conducted on the raw score data. The factors were the four time intervals and five drug levels.</td></tr>
<tr><td rowspan="6">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">8.8</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td></tr>
<tr><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>NR</td></tr>
<tr><td rowspan="2">High</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>NR</td><td>Y</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">The psychological tests employed were designed to test subject's memory, information processing ability, motor coordination and feelings. The tests were always administered in the following order at each session:
1. Backward Digit Span
2. Tapping Board
3. Serial learning
4. Short term memory
5. Delayed recall
6. Simple reaction time
7. Choice Reaction Time
8. Visual Retention Test
9. Subjective Rating Questionnaire: The subjects rated his feelings on 16 scales by drawing a perpendicular line across a horizontal unmarked 100 mm line connecting two adjectives representing the extremes of the condition to be rated. The position of the perpendicular line was measured in mm and used as the score. The 16 adjective pairs fell into each of 4 categories of feelings: mental sedation, physical sedation, tranquilization and attitudes or other feelings which were derived with modifications from Norris (1971)
10. Electroencephalography</td></tr>
<tr><td>Results Q2 and Q6</td><td colspan="14">Digit Span: The results of the analysis indicated a significant Drug x Time interval interaction (P <0.005).
Analysis of this interaction indicated that at the 2-hr test, both doses of o diazepam and the high dose of fentanyl significantly reduced performance below the other two treatments. There were no other significant differences.
Tapping Board: There was a significant overall drug effect, (P <0.005), and Drug x Time interaction, (P <0.01). Follow-up analysis revealed that at 2hrs the effects of the low dose of fentanyl did not significantly differ from the placebo while the high dose of fentanyl and both doses of diazepam significantly lowered performance. Performance returned to the placebo level at the 6th hour test.
Serial Learning: This mental function was found to be highly sensitive to diazepam. While an overall significant drug effect was found (P <0.001), orthogonal contrasts indicated that the effects of fentanyl were significantly less than the effects of diazepam, (P <0.05). Follow-up analysis of the significant Drug x Time interaction, (P <0.01) indicated that only the 2-hr test did the effects of each dose of diazepam differ significantly from placebo. For all other drugs and time no significant effects were observed.</td></tr>
</table>

	Delayed Recall: The results of this test approximately paralleled the results of serial learning. There was a significant main effect for drug type, (P<0.01), Diazepam had a greater effect than fentanyl, (P <0.01).Drug x Time interaction was also significant , (P <0.001). It was found that at 2 hrs each dose of diazepam significantly lowered performance from placebo and from fentanyl. **Short term memory:** The results of the Brown=Peterson test were analyzed by means of 4x4x5 analysis of variance. The additional factor being the four retention intervals tested. The results of this analysis indicated no significant drug effects or drug interactions, P >0.1 in all cases. **Simple Reaction Time**: There were no significant drug effects, (P >0.1) when the median reaction times were used. When standard deviations were the scores, it was found that diazepam significantly increased variability over fentanyl, P <0.001) at the 2-hr test, but no other significant effects were found. **Choice Reaction Time**: Analysis of median reaction time again indicated no significant drug effects or interactions(P >0.05), however, the drug effect did approach significance (P <0.06). Analysis of standard deviation as the response measure showed that diazepam increased response variability more than fentanyl, (P <0.01) **Visual Retention**: Separate analysis conducted on both the number of figures correctly reproduced and on the total number of errors revealed no significant drug effects or interactions, (P >0.2) in all cases. **Subjective questionnaire**: *The drugs produced marked effects on items classified under "mental" and "physical" sedation. All treatments resulted in a highly significant sedative effect at the 0.5 hr post-injection test, (P <0.01). The high doses of both drugs were still effective in producing physical sedation at the 2nd hour post-injection testing, (P <0.01), while the low doses no longer produced significant effects*. The same was true for mental sedation except that the subjects rated themselves as drowsy after both doses of diazepam,(P <0.01). The effect of diazepam was always more marked than that of fentanyl. By 6hrs no statistically significant effects were evident. **Electroencephalography**: Fentanyl showed an initial increase in frontal fast activity, with return to pre-injection levels at the 8th hour for only the high dose. The lower dose showed no prominent changes in any frequency band over time.
Authors' Comments	*On the objective psychological tests, the low dose of fentanyl had no measurable effects at 2hrs post-injection, while both doses of diazepam and the high dose of fentanyl still had a disruptive effect on performance. This was clearly demonstrated in the tapping rate performance. Fentanyl had little effect on memory* while diazepam reduced the ability to learn without increasing forgetting of material already acquired. Recovery was complete by the 6th hour for all treatments according to the psychological tests except for the lagging effects of high dose of diazepam on memory. The electroencephalographic effects of diazepam persisted beyond the end of the testing sessions while those of the high dose of fentanyl recovered by the 8th hour. The lack of EEG changes produced by the low dose of fentanyl correlate with the absence of behavior and subjective effects at 2hrs post-injection. Thus, in the dosage tested, diazepam had more intense and prolonged effects than fentanyl.

Hindmarch I. Some aspects of the effects of clobazam on human psychomotor performance. Br J Clin Pharmacol 1979; 7 Suppl 1:77S-82S.														
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**					
		X												
Research Question	Comparison of the effects of acute night-time doses of clobazam, amylobarbitone sodium, nitrazepam and placebo on choice reaction time (CRT), CFF threshold and stabilometer performance.													
Drug examined	Barbiturates – Amylobarbitone Sodium (Amytal Sodium) 100 mg, oral													
Study Design	Crossover RCT comparing: clobazam, amylobarbitone sodium, nitrazepam and placebo													
Population	**Inclusion Criteria**	Mean age = 28 yrs. Consenting volunteers.												
	Exclusion Criteria	NR												
	Study population characteristics	Twenty volunteers, ten male and ten female, with a mean age of 28 yrs.												
	Generalizability to CMV drivers	Unclear												
Procedures	Each subject received each of the four treatment conditions-clobazam 20mg, amylobarbitone sodium 100mg, nitrazepam 5mg and placebo-presented in identical capsules on a random order basis. The medications were taken at weekly intervals one half-hour before retiring to bed and the subjects presented themselves for testing the following morning.													
Statistical Methods	The treatment differences were computed using a standard two-way analysis of variance. Paired *t* tests were carried out between placebo and active treatment condition for the three assessments measures with probability levels for two-tailed tests.													
Quality assessment	**Internal Validity**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	NR	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	7.9	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
		N	Y	Y	N	Y	Y	Y	Y	Y	Y	NR	Y	NR
	High Quality	**27**	**28**											
		NR	N											
Relevant Outcomes Assessed	1. Choice reaction time **(CRT)**: One of five coloured lights was illuminated at random; the subject responded by pressing the appropriate button to extinguish the stimulus light. The response was taken as the mean time to extinguish 30 stimulus presentations. 2. Critical flicker fusion **(CFF)**: Subjects were required to detect flicker in a set of four light-emitting diodes in foveal fixation. The response measure used was the mean threshold for four presentations. 3. **The Stabilometer** is used as an index of physical performance and muscular balance coordination. Subject had to balance on a horizontal beam pivoted about its center. The response measure taken was time in 'balance' over three separate minute sessions expressed as a percentage of the total task time.													
Results	**CRT:** Amylobarbitone sodium 100 mg produces longer response latencies than placebo on the CRT task. **CFF**: Amylobarbitone sodium, as expected from its sedative action on reticular and cortical systems, depressed the CFF threshold at a P <0.05 when compared with placebo. **Stabilometer:** Stabilometer performance with the barbiturate was not at all different from performance with placebo.(Table G-14)													
Authors' Comments	Clobazam was compared with two established hypnotic sedatives: amylobarbitone sodium and nitrazepam. Clobazam improved early morning performance on a choice reaction test, in contrast to the other two active drugs.													

Table G-14. Mean Results for each Treatment Condition on all Assessment Measures

	Clobazam 20 mg	*Placebo*	*Amylobarbitone sodium 100 mg*	*Nitrazepam 5 mg*
CRT (s)	.419	.435	.441	.471
CFF (Hz)	34.89	36.06	34.36	35.11
Stabilometer (% balance)	15.98	13.02	13.94	21.11

Treatment differences on CRT significant at 0.1% level; treatment differences on CFF significant at 5% level; treatment differences on stabilometer significant at 5% level.

Table 2 *t* values from paired *t* tests between placebo and drug conditions for all assessment measures

	Placebo/amylobarbitone sodium 100 mg	*Placebo/nitrazepam 5 mg*	*Placebo/clobazam 20 mg*
CRT	0.26	2.07 (P<0.1)	1.74 (P<0.1)
CFF threshold	–2.51 (P<0.05)	0.86	1.20
Stabilometer	0.83	2.57 (P<0.02)	2.05 (P<0.1)

<table>
<tr><td colspan="15">Jeffrey DW. Modification of arousal and performance in young and elderly men by dextroamphetamine. Proc Annu Conv Am Psychol Assoc 1972; 7(Pt 2):659-60.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td colspan="2">3</td><td colspan="2">4</td><td colspan="2">5</td><td colspan="2">6</td><td colspan="2">7</td><td colspan="2">8</td><td>9</td></tr>
<tr><td></td><td>X</td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td colspan="2"></td><td></td></tr>
<tr><td>Research Question</td><td colspan="14">To manipulate arousal in young and elderly Ss using the stimulant drug dextroamphetamine, and determine the effect of changes in arousal as indicated by GRS and visual RT.</td></tr>
<tr><td>Drug examined</td><td colspan="14">Stimulant - Dextroamphetamine 5mg – oral vs placebo</td></tr>
<tr><td>Study Design</td><td colspan="14">Crossover (each subject served as their own controls) trial in which 8 elderly and 10 young subjects received dextroamphetamine and placebo.</td></tr>
<tr><td rowspan="4">Population</td><td colspan="2">Inclusion Criteria</td><td colspan="12">Eight elderly Ss, ages 66-78 and 10 young Ss, ages 21-33. All had previously served as Ss in psychophysiological experiments. All were medically screened prior to being run.</td></tr>
<tr><td colspan="2">Exclusion Criteria</td><td colspan="12">NR</td></tr>
<tr><td colspan="2">Study population characteristics</td><td colspan="12">Eight elderly Ss, ages 66-78 (M=70.5)
Ten young Ss, ages 21-33 (M=22.9)</td></tr>
<tr><td colspan="2">Generalizability to CMV drivers</td><td colspan="12">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="14">All completed two 30-min testing session on alternate days according to a balanced design. Testing began 90 minutes after Ss were administered either 5 mg. of dextroamphetamine in elixir form or 5 mg. of a placebo liquid. Ss were not told what drugs were being used.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">2 X 2 X 4 analysis of variance
t tests based on the grand mean RTs</td></tr>
<tr><td rowspan="6">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">6.4</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td></tr>
<tr><td>N</td><td>N</td><td>N</td><td>NR</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>NR</td><td>N</td><td>NR</td></tr>
<tr><td rowspan="2">Moderate Quality</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>NR</td><td>Y</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">1. The reaction times (RTs) (visual) were conducted using a simple telegraph type reaction key taped to the right arm of the chair occupied by the Ss.
2. The Galvanic skin response (GSRs) was recorded from electrode placement on the tip of the left forefinger and a curved armband placed on the upper portion of the left arm.</td></tr>
<tr><td>Results</td><td colspan="14">The results indicated that reaction times (RTs) for the two groups differed as expected, with the elderly Ss responding more slowly than the young. Both groups also responded more quickly under Dexedrine than placebo condition. The elderly responded proportionally faster under dextroamphetamine than placebo, than did the young Ss, and these results would support an arousal or activation explanation of behavioral slowing with age.
The age and drug differences above were significant ($p < 0.01$) using a 2 X 2 X 4 analysis of variance. There was no significant effect of time in the experiment. The proportional differences were also significant ($p < 0.01$) as analyzed by t tests based on the grand mean RTs. The fastest 25 and slowest 25 trials were averaged and compared and the same relationships were found to hold.
Galvanic skin response (GSRs): Examination of the GSRs by quartile indicated that under the placebo condition, average GSRs were slightly reduced in amplitude with time in the experiment. This reduction in amplitude over time was greater for the elderly than for the young Ss. Under the dextroamphetamine condition, reduction in GSR amplitude over time was less ans was similar for both elderly and young Ss.
Examination of GSRs for the fastest and slowest trials indicated that for both old and young Ss GSR amplitude was greater for slow than fast responses and was greater under the effects of dextroamphetamine than the placebo. However the effect of dextroamphetamine on GSR amplitude was greater for the young than the elderly.
The results suggest that dextroamphetamine in the dose level used in this experiment, i.e., 5mg, had a greater effect on averaged GSRs for the young than the elderly Ss, whereas, he effect on RT was greater for the elderly than the young.</td></tr>
<tr><td>Authors' Comments</td><td colspan="14">The authors conclude that their results suggest that therapeutic use of small amount of stimulants with elderly individuals may facilitate simple performance and functioning. They also note, however, that previous studies indicate that dextroamphetamine effects over time tend to habituate and result in no real effects in terms of psychological and physiological indices. The authors also note that their results suggest that behavioral slowing, reported as a consistent correlate of aging, may well be related to a reduction in the number of functional neural cells as one ages.</td></tr>
</table>

<table>
<tr><td colspan="15">Kerr B, Hill H, Coda B, Calogero M, Chapman CR, Hunt E, Buffington V, Mackie A. Concentration-related effects of morphine on cognition and motor control in human subjects. Neuropsychopharmacology 1991 Nov; 5(3):157-66.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td></tr>
<tr><td></td><td>X</td><td></td><td>X</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="14">1) To evaluate the sensitivity of each cognitive and motor function measure to morphine, a mu-receptor-selective opioid agonist.
2) To examine the relationships between the magnitude of cognitive and motor effects and concentrations of morphine in plasma.</td></tr>
<tr><td>Drug examined</td><td colspan="14">Opioids – Morphine continuous infusion (Opioids infusion via an IVAC volumetric infusion pump Model 1500 that was controlled by a Macintosh computer). Target concentration plateaus: 20, 40, and 80 ng/ml</td></tr>
<tr><td>Study Design</td><td colspan="14">Crossover study in which 15 healthy volunteers received morphine and saline.</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Age = 21 to 37 yrs. Healthy male volunteers. None reported a history of alcohol or drug abuse and none was currently using medications of any kind. Informed consent.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">NR</td></tr>
<tr><td>Study population characteristics</td><td colspan="13">15 healthy male volunteers. Body weight ranged from 55.4 to 98.6 kg; all were within ±10 per cent of normal weight for height.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="14">Subjects remained seated in a hospital bed inside a sound-attenuated testing chamber throughout each pretest and infusion session. Each subject participated in a pharmacokinetic tailoring session involving bolus doses of morphine and another session for task battery practice. Each subject then participated in infusion sessions with morphine and saline infused on different days. The order of drug treatment was counterbalanced across subjects and a minimum of 7 days separated sessions for each subject.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Morphine and saline results were compared using 2 x 3 (Drug by Infusion Period) repeated-measure analysis of variance (ANOVAs). Planned pairwise comparisons (two-tailed) compared results from the low, medium, and high target plasma concentration periods to their corresponding saline infusion hours.</td></tr>
<tr><td rowspan="6">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">8.0</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td></tr>
<tr><td>N</td><td>NR</td><td>NR</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td></tr>
<tr><td rowspan="2">High Quality</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>N</td><td>Y</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">1. <u>Motor performance</u>:
- Tapping: Subjects tapped a key using the index fingers of alternate hands, the preferred hand, and the nonpreferred hand as quickly as possible for 7-second trials.
- Isometric force: subject held a small, high-precision isometric force transducer between the index/middle fingers and thumb, maintaining a constant position. Subjects performed 5 tasks. In most cases a visual representation of force magnitude versus time appeared on the computer monitor.
(1) Maximum force
(2) Maintenance of low constant force with visual feedback
(3) Maintenance of low constant force without visual feedback
(4) Fast repetitive changes between two submaximum forces
(5) Targets
2. Visual perception (Lines and letters): The subject indicated whether a sinusoidal display terminated above or below a reference line or completed a letter identification task administered before starting the RSVP passages.
3. <u>Cognitive performance</u> (Verbal comprehension and memory(both immediate and delayed):
- Rapid Single Visual Presentation (RSVP): Words are presented individually on a computer screen. Following the presentation of a passage and a brief distraction task, comprehension tested with questions about the content of the passage. Time required to read words recorded.
- End-of-day questions: Final memory test. Questions referred to narrative passaged read during the practice hour and each of the four infusion steps.</td></tr>
<tr><td>Results Q2</td><td colspan="14">Tapping: There was a slight (0.3 taps per second) decrement in preferred hand tapping at the high target concentration of morphine. The drug main effect was significant ($p < 0.05$); pairwise comparisons confirmed a significant difference at the high target concentration, ($p < 0.001$).(Table G-18)
Isometric force (Table G-19): There was no indication that morphine influenced either maximum force or the number of times subjects were able to change force levels in 20 seconds However, the infusion Period main effects was significant in the analysis for maximum force ($p < 0.05$).This order effects indicate that, averaged across saline and morphine, performance improved and then decreased across the hours of infusion testing. Morphine did affect the three force tasks that require more precise motor control.
Visual perception (lines): Subjects found the visual perception task easy and extremely boring. No subject missed more than 2 of the 96 possible during the four infusion hours.</td></tr>
</table>

	RSVP (Table G-16**)**: Median time required to read a word at the different target levels of morphine, compared with the reading times at the comparable hours on the saline infusion day: analysis of variance tests yielded significant main effects of Drug ($p < 0.01$), and Infusion period ($p < 0.05$). There was also a significant Drug X Infusion Period interaction ($p < 0.001$). Table G-20 reports mean proportion correct answers for the low, medium and high target plasma concentrations of morphine. Neither the Drug main effect nor the Drug by infusion Period interaction proved statistically reliable ($p > 0.05$). These results together with the reading-time data indicate that *subjects were slowed considerably in their ability to take in and process information during morphine infusion*, *but their immediate memory and comprehension of that information was not impaired.* **End-of-day-Answers**: *Morphine did not impair subjects' ability to answer questions immediately after they read the passages, it did impair their later recall of textual informations (P <0.01).* All subjects performed almost perfectly on the letter identification task at all target plasma concentrations of morphine, and this indicates that the subjects had no difficulty reading the computer screen.
Results Q4	The tree target concentration plateau for morphine was 20, 40 and 80 ng/ml. **Tapping (**Table G-18**):** *There was a small (0.3 taps per second) decrement in preferred hand tapping at the highest target concentration of morphine. The drug main effect was significant (p <0.05); pairwise comparisons confirmed a significant difference at the high target concentration (p <0.001*) The nonpreferred hand tapped faster under morphine than saline for the medium target concentration ($p < 0.05$). Investigators attributed this unexpected finding to the unusually slow saline tapping rate during that period of the saline infusion rather than a true difference from morphine. There were no reliable differences between morphine and saline for the bimanual task, indicating that morphine does not influence the ability to coordinate the hands in the task at the concentration studied. **Isometric force (**Table G-19**):** For the targets task, there was a significant Drug by Infusion Period interaction ($p < 0.001$). At the low target concentration, the number of targets hit was higher with morphine than saline ($p < 0.05$) *However, at the high target concentration, morphine impaired performance (p <0.05). The most serious drug effects occurred during the tasks that required the maintenance of low levels of force, with greater deficits when subjects could not rely on vision.* In the analysis for maintenance with vision and without vision, absolute error was larger for morphine than saline at the high target concentration ($p < 0.05$ and $p < 0.001$, respectively).This suggests that vision provides important cues when other sources of information become unreliable. **RSVP (**Table G-16**)**: *The lowest target concentration of morphine did not impair reading speed, but performance deficits occurred at the medium and high target levels and increase with plasma concentration.*
Authors' Comments	The authors found strong effects of morphine on some (but not all) cognitive measures and motor function tasks during the steady-state infusions. The degree of impact of this mu-receptor-selective opioid on the drug –sensitive measures was related to plasma concentration of morphine. Morphine also had a strong negative effect on delayed memory. Physicians prescribing morphine on a long-term basis may wish to caution patients that morphine may impair aspects of cognition and motor function. Investigators temper their conclusions about the negative influence of morphine on cognition and motor control with a reminder that Investigators tested healthy volunteers who were not in pain. In patients who are in pain, the presence of pain might cause cognitive and motor effects that would be reduced by the opioids administered to reduce pain. Such effects could occur as a consequence of the distraction caused by pain or as a consequence of the effects of stress on the hypothalamic-pituitary-adrenocortical axis.

Table G-15. Standard Hour Long Testing Sequence

Time	Task
1–5 min	Three tapping tasks
6–8 min	Visual perception task (lines)
9–30 min	Five force tasks
31–35 min	Apparatus switch
36–37 min	Visual perception task (letters)
38–45 min	RSVP task narrative passage
46–55 min	RSVP task expository passage
56–60 min	Apparatus switch

Table G-16. Summary of Significant Decrements on Cognitive and Motor Tasks

Test	
Control vision tasks	
Visual perception (letters)	None
Visual perception (lines)	None
Tapping	
Preferred hand tapping	High[a]
Nonpreferred hand tapping	None
Bimanual tapping	None
Isometric force	
Maximum force	None
Fast repetitive changes	None
Targets	High
Low force/visual feedback	High
Low force/no visual feedback	High
RSVP	
Reading time	Medium and high
Answers to questions	None

[a] Refers to target concentration of morphine that produces significant decrements in performance.

Table G-17. Average Measured Plasma Morphine Concentrations

Table 3. Average Measured Plasma Morphine Concentrations (ng/ml) for Individual Subjects at Different Target Concentrations[a]

Subject No.	Morphine 20 ng/ml	Morphine 40 ng/ml	Morphine 80 ng/ml
1	26.6 (1.6)	55.3 (2.6)	111.7 (8.2)
2	22.5 (2.7)	44.4 (5.3)	92.5 (9.8)
3	22.0 (1.7)	43.1 (3.8)	92.1 (3.7)
4	20.0 (6.3)	51.6 (1.9)	97.7 (6.0)
5	17.4 (3.2)	31.9 (2.5)	65.3 (6.8)
6	12.5 (1.8)	30.4 (1.0)	62.7 (2.7)
7	21.3 (1.0)	38.8 (2.7)	79.1 (0.3)
8	24.7 (3.4)	48.9 (9.0)	73.1 (3.2)
9	19.7 (3.3)	40.5 (3.9)	84.6 (6.1)
10	13.3 (2.8)	31.5 (4.1)	75.9 (1.8)
11	21.7 (1.6)	40.0 (4.5)	60.4 (11.6)
12	21.1 (1.6)	42.0 (2.0)	73.1 (11.4)
13	22.0 (1.4)	42.0 (5.9)	83.1 (7.4)
14	23.5 (4.8)	39.2 (0.6)	86.7 (7.9)
15	16.3 (2.6)	33.1 (2.3)	66.1 (9.2)

[a] Values are means (SD) of five plasma samples at each plateau.

Table G-18. Mean (SD) Number of Taps per Second during Morphine Infusion

	Saline	Morphine
	Preferred hand	
L	5.05 (0.49)	5.01 (0.72)
M	5.12 (0.59)	5.02 (0.61)
H	5.16 (0.62)	4.86 (0.58)
	Nonpreferred hand	
L	4.42 (0.78)	4.27 (0.73)
M	4.32 (0.76)	4.55 (0.82)
H	4.34 (0.75)	4.45 (0.87)
	Bimanual	
L	7.67 (1.24)	7.46 (1.14)
M	7.68 (1.42)	7.66 (1.15)
H	7.77 (1.32)	7.30 (1.47)

Table G-19. Mean (SD) Scores for Force Tasks during Morphine Infusion

	Saline	Morphine
	Maximum force (Newtons)	
L	108.8 (21.8)	110.3 (21.8)
M	111.3 (22.9)	114.0 (22.6)
H	108.3 (20.3)	106.6 (20.4)
	Fast repetitive changes (number in 20 sec)	
L	104 (35.3)	110 (32.4)
M	104 (32.1)	106 (34.8)
H	105 (34.3)	103 (36.2)
	Targets (Number hit of 10 possible)	
L	7.1 (1.25)	8.0 (1.13)
M	7.5 (1.19)	7.5 (1.36)
H	7.7 (0.98)	6.6 (1.40)
	Maintenance with vision (Absolute error in Newtons)	
L	0.2964 (0.089)	0.3013 (0.713)
M	0.3249 (0.120)	0.3558 (0.125)
H	0.3246 (0.127)	0.6281 (0.420)
	Maintenance without vision (Absolute error in Newtons)	
L	1.0792 (0.544)	0.9843 (0.303)
M	1.2554 (0.492)	1.1887 (0.621)
H	0.9747 (0.252)	2.0721 (0.882)

Table G-20. Mean (SD) RSVP Proportion Correct During Morphine Infusion

	Saline	Morphine
L	0.79 (0.21)	0.82 (0.17)
M	0.85 (0.14)	0.65 (0.22)
H	0.71 (0.26)	0.77 (0.23)

<table>
<tr><td colspan="15">Kopriva K, Frantik E, Horvath M. Pentobarbital effect on performance in monotonous conditions not prevented by compensatory effort. Act Nerv Super (Praha) 1974 Aug;16(3):176-8.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td></tr>
<tr><td></td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="14">To examine the effects of pentobarbital on performance in monotonous conditions not prevented by compensatory effort.</td></tr>
<tr><td>Drug examined</td><td colspan="14">Barbiturates: Pentobarbital 150 mg / 70kg , oral</td></tr>
<tr><td>Study Design</td><td colspan="14">Randomized, double-blind, controlled study in which the effects of pentobarbital were compared to those of placebo.</td></tr>
<tr><td rowspan="4">Population</td><td colspan="2">Inclusion Criteria</td><td colspan="12">Professional drivers</td></tr>
<tr><td colspan="2">Exclusion Criteria</td><td colspan="12">NR</td></tr>
<tr><td colspan="2">Study population characteristics</td><td colspan="12">90 professional drivers</td></tr>
<tr><td colspan="2">Generalizability to CMV drivers</td><td colspan="12">Low/Moderate?</td></tr>
<tr><td>Procedures</td><td colspan="14">The subject was seated in an armchair with phones on his head through which weak, short sound signals (clicks) differing in spatial location were heard in irregular intervals. The subject had to press a button to stimuli from right and left, which represented 50% of all stimuli, and to ignore midline stimuli. The main part of the investigation consisted of a control program (12 min, 100 stimuli in relatively short intervals, 5-9 secs) and of the monotonous program (65 min, 250 stimuli in long intervals, 8-25 secs). The capsule which contains either pentobarbital in a dose of 150mg/70 kg or placebo was given to the subject immediately before the start of the monotonous program in conditions of a double-blind experiment.
An effort to compensate the drug effect was induced by the following instruction. Before administering the capsule, the subject was told that the drug he was going to take might elicit in some people drowsiness and affect adversely performance. He was also informed that the course of physiological functions after drug application permits to determine in a relatively short period of time whether the drug has any effect or not and that this information would be transmitted to him by a light signal in time, so that he would be prepared to counteract any disturbing effect of the drug. After the first 13 min. of the monotonous program (i.e., 14 min after ingesting the table) a sign appeared in the subject's visual field saying "acts" (positive instruction for compensation) or "does not act" (negative instruction) which remained lit up until termination of the experiment. The alternative was determined beforehand according to a given random program)</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Statistical processing was performed with a two-factor analysis of covariance (adjustment of post-drug performance for different initial levels)</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>Yes</td><td>NR</td><td>NR</td><td>Yes</td><td>NR</td><td>Yes</td><td>Yes</td></tr>
<tr><td rowspan="2">5.4
Moderate Quality</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td>NR</td><td>Yes</td><td>NR</td><td>NR</td><td>No*</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>NR</td><td>NR</td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Reaction time (auditory)
Two qualitative different types of errors are evaluated separately: errors of omissions to easily discriminate signals and errors of commission.
After termination of the experiment the subject had to fill-in questionnaires pertaining to his subjective perception of the drug effect on mood and performance and to his compensatory effort.</td></tr>
<tr><td>Results</td><td colspan="14">Table G-21 shows the statistically verified effect of pentobarbital and the virtually nil effect of the instruction for compensation on errors of omission. With regard to error of commissions the situation was reversed – no drug effect could be evidenced while the influence of the instruction was apparent in the sense that subject who were given positive instructions for compensation had significantly more false positive reactions.
The increase in errors of omission under the effect of pentobarbital coincides with the anticipated inhibitory action of the drug. It is interesting that this effect was not in the least affected by the instructions for compensation. On the other hand, the fact that instructions influenced errors of commission indicates that the subjects did not simply ignore it. The questionnaire revealed, too that the instruction had been accepted by the subjects (a significantly higher compensatory effect and perception of the drug effect at the positive instruction). *The errors of omission to easily discriminate signals are a measure of the incidence of short-term vigilance failure*s (blocks, micro sleeps). Thus frequency of blocks during the monotonous program was not influenced by increased effort in our sample. The increase in errors of commission under the influence of positive instruction fro compensation may be related to a shift in discrimination criterion. The subjects in their attempt to lessen the risk of the anticipated "miss" tended to respond to stimuli that were difficult to discriminate for them rather than to ignore them.</td></tr>
<tr><td>Authors' Comments</td><td colspan="14">The results of this study suggest that the general belief that the human is able to compensate by his own effort the disturbing effect of foreign substances on performance does not necessarily apply to monotonous situations.</td></tr>
</table>

Table G-21. Results

	P IN	− −	− +	+ −	+ +	Whole sample	s_{res}	Analysis of covariance		
	N	22	20	21	21	84		Drug	Instruction	Interaction
%10	X	7.4	10.1	5.4	5.8	7.1	9.1	$F = 6.1$ $p < 0.05$	$F < 1$ n.s.	$F < 1$ n.s.
	Y	19.8	21.6	27.5	27.1	24.0	18.4			
%01	X	9.2	11.9	9.5	15.3	11.5	13.1	$F < 1$ n.s.	$F = 5.2$ $p < 0.05$	$F = 1.5$ n.s.
	Y	10.8	17.4	11.4	21.8	15.3	14.5			

<table>
<tr><td colspan="15">Korttila K, Linnoila M. Psychomotor skills related to driving after intramuscular administration of diazepam and meperidine. Anesthesiology 1975 Jun; 42(6):685-91.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td></tr>
<tr><td></td><td>X</td><td></td><td></td><td></td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="14">To examine the effects of Meperidine on psychomotor skills related to driving.</td></tr>
<tr><td>Drug examined</td><td colspan="14">Opioids – Meperidine 75mg (intramuscular injection)</td></tr>
<tr><td>Study Design</td><td colspan="14">Randomized, double-blind, crossover trial in which 11 healthy volunteers were tested before, and 1, 3, 5, and 7 hours after intramuscular injection of saline, 10 mg diazepam, or 75 mg meperidine.
The late effects of meperidine were tested in five other subjects 12 and 24 hours after the injection.</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Healthy student volunteers. Their medical history indicated good health, and creatinine, alkaline phosphatase, and serum transaminases were normal. None of the subject had had any previous experience with diazepam and meperidine or had taken any medicine for at least a month prior to the experiment. Most used alcohol only occasionally. Informed consent was obtained for the procedure.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">NR</td></tr>
<tr><td>Study population characteristics</td><td colspan="13"><u>Variable</u> — <u>Values</u>
n — 11
Age: (yrs.) mean ±SD — 25 ±2.6
Height (cm) mean ±SD — 173.0 ±9.5
Weight (kg) mean ±SD — 67 ±11
Gender M/F — 8 / 3</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="14">Saline placebo, diazepam (Valium), 10mg, or meperidine hydrochloride (Petidin) 75mg, was injected in a volume of 2ml into the muscle of the left thigh at two-week intervals in a double-blind, crossover, randomized (Latin square) fashion. Patients were tested in the morning 1 hour before and 1.3.5.and 7 hours after each treatment. They stayed in a horizontal or slightly recumbent position during the injection and until the one-hour test period.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Additivity of the results and within-cell variances were checked, and thereafter the two-way analysis of variance and student's t test were used for statistical analysis of the data.</td></tr>
<tr><td rowspan="6">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">8.6</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td></tr>
<tr><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>?</td><td>Y</td><td>N</td></tr>
<tr><td rowspan="2">High</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>N</td><td>Y</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">1. Subjective assessment: After each test day the subjects were asked whether they thought they had received a tranquilizer, stimulant, or placebo. At every test period they were asked whether they felt tired and how well they felt they could drive. After the whole experiment the subjects were asked which treatment had induced the most pleasant and unpleasant sensation, which had caused the greatest sedative effect and which the greatest pain at the injection site.
2.Psychomotor tests:
1. Reactive skills: Cumulative reaction time and number of mistakes were recorded.
2. Coordinative skills: Two tracking tasks were used to measure hand-eye coordination. The number of mistakes and mistake percentages were recorded. Coordination test I was driven with affixed speed. Coordination test II was driven at a free speed, and the driving time was recorded.
3. Critical flicker-fusion frequency was measured at every test period. Each subject was instructed to announce when a flickering red light (diameter 3 mm) at a distance of 90cm stop flickering.</td></tr>
<tr><td>Results Q2 and Q6</td><td colspan="14"><u>Subjective assessments and side effects</u>: (Table G-22, Table G-23, Table G-24)
Half of the patients injected with diazepam and 73% of those injected with meperidine considered the drug to be a tranquilizer, while more than half of the subjects regarded saline solution as a placebo. Seven hours after the injection none of the subjects injected with saline placebo was tired, but 9% of those injected with diazepam or meperidine felt tired. There was no recurrence of clinical sedation after that time.
The volunteers' conception of their driving abilities were the most pessimistic 1 to 5 hours after injection of meperidine , but at 7 hours 82% of those injected with either diazepam or meperidine considered their driving ability to be normal. Treatments with meperidine induced the most unpleasant feeling and the greatest sedation and fatigue. The intensities of pain at the injection site were similar after diazepam and meperidine. After both treatments the thigh became slightly sore and remained that way for the rest of the day, but soreness disappeared by the next morning. Side effects were more common with meperidine. Two of the volunteers (18%) injected with meperidine experienced syncope after standing up 1 hour after the injection and were unable to perform the test at that time.
Despite pre-test training on the apparatus, many subjects continued to improve their performances, especially after the saline solution.</td></tr>
</table>

	This suggests that a training effect continued during the actual trial. Due to the Latin Square this must have influenced all treatments similarly, possibly increasing the standard deviation in each treatment. **Test performances** **Reactive skills**: Both diazepam and *meperidine significantly impaired the cumulative reaction times*, *compared with saline solution* (two-way analysis of variance; diazepam P <0.001; meperidine P <0.01), but after the saline injection there was a tendency for improved performances throughout the experiment. *The cumulative reaction times remained significantly (P <0.05) worse, compared with saline solution for 3 hours after injection of meperidine* and for 5 hours after injection of diazepam. The number of mistakes did not change significantly after any treatment. **Coordinate skills**: Both diazepam and *meperidine significantly* (two-way analysis of variance: P <0.01) *impaired the parameters measured in coordination test I*, *compared with saline solution*. The mistakes percentages 5 hours after both diazepam and meperidine were still significantly (P <0.05) higher than after saline placebo, but at 7 hours the results were similar after the two treatments. Driving time did not change significantly. However, subjects treated with saline solution or diazepam had slightly longer driving times after their injections than before, whereas meperidine tended to make the subjects use a faster speed. **Critical Flicker- fusion frequency**: *Only meperidine significantly* (two-way analysis of variance: P <0.001) *impaired flicker-fusion discrimination*, *compared with saline placebo*. *The ability to discriminate flickering light after meperidine was significantly (P <0.05) worse for 3 hours after the injection and had not yet reached the level of saline placebo at 7 hours*. **Late effects of meperidine**: Since the results of the choice-reaction and flicker-fusion tests 7 hours after meperidine were still worse than after saline solution, Investigators tested another five volunteers of similar ages, weights, heights, and education levels with meperidine. They practised for 2 hours to obtain a constant level of performance and were tested before the injection in the evening. The test battery was then repeated 12 and 24 hours later, the next morning and the following evening. *Twelve hours after the injection the parameters measured in coordination test I were significantly (P <0.05) worse and cumulative reaction times slightly worse than those measured at the preinjection tests. The ability to discriminate the fusion of flickering light was no longer affected at 12 hours. All the results at 24 hours were similar to those measured before the injection of meperidine.* **Drug levels in serum:** The highest concentration of diazepam (295 ±82 ng/ml) and meperidine (179 ±66 ng/ml) in serum (means ±SD) were measured 1 hour after injection, after which they declined as function of time with both drugs. Average biological half-lives for diazepam and meperidine were 12 and 4 hours, respectively, as semilogarithmically calculated from the mean values at 3,5, and 7 hours. Those subjects having syncope after meperidine did not have higher concentrations of meperidine in their sera, but nausea and dryness of the mouth seemed to correlate with the meperidine level in the serum. Effects of meperidine: In this study the harmful effets of meperidine on psychomotor performance could be measured for 12 hours, but 24 hours after the injection the performances of all five subjects resembled their preinjection performances. In the present study 2 subjects experienced syncope. This complication should be remembered when patients received the drug as premedication in anesthesia before being fully prepared for surgery.
Authors' Comments	*Meperidine impaired reactive skills for as long as 3 hours and flicker-fusion discrimination and coordination skills for as long as 12 hours. It is concluded that patients should not drive or operate machinery for at least 24 hours after receiving 75 mg meperidine intramuscularly.* Because of the possibility of syncope after intramuscular administration of meperidine and because of the prolonged impairment of psychomotor skills the drug should not be used in ambulatory practice. One must remember that the results of the present study were obtained in young healthy subjects; the effects of the drug in old or ill patients could be more harmful and more prolonged.

Table G-22. Volunteers Conception of Treatments

Treatment	Conception of Volunteers		
	Placebo (Per Cent)	Tranquilizing Drug (Per Cent)	Stimulating Drug (Per Cent)
Saline solution	64	18	18
Diazepam	36	64	—
Meperidine	9*	73	18

* $P < 0.05$ compared with saline solution ($\chi^2 = 4.91$).

Table G-23. Comparative Subjective Assessments of 11 Volunteers after IM Diazepam, Meperidine, or Saline

	Saline Placebo (Per Cent)	Diazepam, 10 mg (Per Cent)	Meperidine, 75 mg (Per Cent)
Most pleasant treatment	46	27	27
Most unpleasant treatment	9	18	73
Greatest sedation and tiredness	—	18	82*
Most painful injection	—	45	55

* $P < 0.05$ compared with saline placebo ($\chi^2 = 6.54$).

Table G-24. Side Effects in 11 Volunteers after IM Diazepam, Meperidine, or Saline

	Saline Placebo (Per Cent)	Diazepam, 10 ng (Per Cent)	Meperidine, 75 mg (Per Cent)
Syncope after standing up	—	—	18
Pain at injection site	9	64	55
Nausea	9	—	18
Vertigo	18	—	18
Dry mouth	—	—	36
Headache	—	—	27

<table>
<tr><td colspan="15">Linnoila M, Hakkinen S. Effects of diazepam and codeine, alone and in combination with alcohol, on simulated driving. Clin Pharmacol Ther 1974 Apr; 15(4):368-73.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td></tr>
<tr><td></td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="14">To examine the effects of diazepam and codeine, alone and in combination with alcohol, on simulated driving and to examine drug-induced risks for traffic. Interest was focused on emergency situation and on driving in monotonous surroundings.</td></tr>
<tr><td>Drug examined</td><td colspan="14">Opioids – Codeine phospate 50 mg, oral</td></tr>
<tr><td>Study Design</td><td colspan="14">Double-blind, controlled study in which the effects of diazepam were compared to those of codeine and placebo.</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Seventy professional drivers from Finnish Army, aged 19 to 22 years, volunteered for the study. They had been carefully tested before they were chosen for the motorized troops. None of the subjects had used any drugs during the 2 weeks preceding the experiment; all of them used alcohol occasionally</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">NR</td></tr>
<tr><td>Study population characteristics</td><td colspan="13">The subjects were young professional drivers in compulsory military service in motorized troops.
70 subjects were divided into 7 tests groups of 10 subjects each (Error! Reference source not found.)</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Low/moderate?</td></tr>
<tr><td>Procedures</td><td colspan="14">Before the experiment every subject was allowed to train with the simulator until he felt comfortable with it.
Every subjects drove for 40 minutes beginning 30 minutes after the simultaneous administration of drug and drink. Drugs were administered double blind in identical gelatin capsules, containing 5 mg of diazepam, 25 mg of codeine phospate or lactose placebo. Every subject received 2 capsules in combination with an alcoholic or nonalcoholic bitter drink.
Subjects were told to adapt speed to surroundings and traffic.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">The data were cross tabulated and analyzed by means of student's t test.
The results of the zero subjects were used for reference in the statistical analysis of the data</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>NR</td><td>NR</td><td>NR</td><td>Yes</td><td>NR</td><td>NR</td><td>Yes</td><td>NR</td><td>NR</td><td>No*</td><td>NR</td><td>Yes</td><td>Yes</td></tr>
<tr><td rowspan="2">4.8
Low Quality</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td>NR</td><td>Yes</td><td>NR</td><td>NR</td><td>No*</td><td>Yes</td><td>Yes</td><td>No*</td><td>No*</td><td>Yes</td><td>NR</td><td>Yes</td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">1. Simulated driving: The simulator was a modified Sim-L-car, which operated by a shadow projection of a point source of light. The simulated moving roadway presented a built-up area with four intersections. Emergency situations occurred twice during every experiment in which a car drove from a yard in front of the experimental car. The variables recorded were:
• Electric recordings: Steering wheel reversals, number of times brakes were applied, number of times clutch was used, number of times turning signals was used, continuous recording of speed, continuous recording of shifting, brake reaction time and pulse frequencies.
• Recording from a TV monitor: Number of neglected instructions, number of collisions and driving off the road.
2. Subjective assessments: After the simulated driving the subjects were asked how they felt about their performance and the nature of their treatment. They were also asked to assess their average driving speed.</td></tr>
<tr><td>Results Q2</td><td colspan="14">Controls: The zero subjects (no drug, no drink) generally felt their performance was normal. One collision occurred in the zero group.
Sixty per cent of the placebo subjects (placebo capsule, placebo drink) felt that their performances were impaired, and that their treatments was a tranquilized and alcohol; they assessed their speed less accurately; the number of steering wheel reversal s was higher (p <0.005) than in the zero group; they switched on turning signal much later (p <0.005) than the zero subjects; they neglected instructions 3 times while approaching the intersection. Three collisions occurred in the placebo group.
The real average driving speeds in both control groups were roughly equal. In both the zero and the placebo subjects there generally was an increase of pulse rate in response to emergencies.
Many of the placebo subjects behaved as if they were under the influence of alcohol, and because normal drivers are generally not treated with placebos, the results of the zero subjects were used for reference in the statistical analysis of the data
Effects of codeine: Subjective feelings of performance were slightly impaired after 50 mg of codeine, which was considered both a tranquilizer and a stimulant of 40% of the C subjects (codeine phospate 50 mg, placebo drink). Sixty per cent of the C subjects thought they had also received alcohol. The average speed of the C subjects did not differ from that of the zero group, but the C subjects slightly overestimated their speed. The number of steering wheel reversals was less (p <0.005) than in the zero group. During emergencies the pulse reactions in the C group were smaller (p <0.01) than those in the zero group.
The C subjects caused collisions more often (p <0.001) than the zero group, but only 3 of them drove off the road.</td></tr>
<tr><td>Authors' Comments</td><td colspan="14">Placebo increased the inaccuracy of speed estimation.
Codeine, 50 mg, can increase risks in driving in both emergency situations and monotonous surroundings. The greatest increase in collisions was after codeine 50mg.
The adaptation of the central nervous system to drug was probably avoided, since the experiments were performed soon after administration of the drugs. Because a majority of the placebo subjects believed that they received active treatments, it can be concluded that the "placebo effect" was present, and the double-blind design maintained.</td></tr>
</table>

<table>
<tr><td colspan="15">Logsdon R. Secobarbital and perceptual processing. Acta Psychol (Amst) 1984 MAR; 55(2):179-93.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td></tr>
<tr><td></td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="14">To examine acute secobarbital dose treatments effects on choice reaction time in a visual character recognition task.
1) To verify a previously observed interactions between the effects of the drug and factors affecting the efficiency of visual stimulus processing.
2) To investigate a two-stage, additive model of stimulus encoding
3) To evaluate the hypothesis that barbiturates treatments affect performance by placing selective stress on the first and earlier encoding activities.</td></tr>
<tr><td>Drug examined</td><td colspan="14">Barbiturates – Secobarbital sodium, medium dose (2.0 mg / kg) or high dose (2.9 mg / kg), oral</td></tr>
<tr><td>Study Design</td><td colspan="14">Crossover study in which 18 male volunteers received medium or high dose of secobarbital and placebo</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Age = 21 to 35 yrs. Each volunteer was screened initially by a written questionnaire, then by a physical exam, to rule out individuals who might be adversely affected by secobarbital. All subjects had normal vision or normal corrected vision, and none had a significant history of emotional disturbance, heavy alcohol or drug use, or head injury. Informed consent.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">NR</td></tr>
<tr><td>Study population characteristics</td><td colspan="13">Eighteen male college students aged 21- 35 years.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="14">Each subject reported to the laboratory for a two-hour practice session during which he familiarized himself with the task. The practice session was followed by three test days (separated by at least 48 hrs), on which subject received either placebo, medium or high dose of secobarbital, all prepared in identical capsules. Order of presentation of the drug was arranged in a Latin Square design to balance practice effects.
Before each of the three test days, subjects were instructed not to ingest any alcohol for at least 12 hours prior to the administration of the drug treatment. As an added precaution, on each test day subjects were evaluated from blood alcohol concentration (BAC) with a breathalyzer to insure that the BAC was zero.
Subjects were seated 75 cm from a screen. They were instructed to hold the index finger of each hand slightly above one of 2 micro switches (Z or / on the keyboard).Closure of either the right or left micro switches signaled a response. The time between the onset of the stimuli and switch closure was recorded in msec. Beginning thirty to forty min. after the administration of the drug, two test sets of 192 trials were performed. Time required fro performance of the two test sets was about 45 min.
Variables manipulated and the levels of each were secobarbital dose (placebo, medium, high), visual stimulus degradation (intact, degraded), character difficulty (easy, difficult), angle of orientation (upright, 180 degrees rotated), and reversal (normal, mirror-image). The decision to include character difficulty as a variable in the task was based on an analysis of pilot data which indicated that from a set of six, one group of letters (G,L, and J) produced consistently longer reaction times than another group (R,P, and F).
After testing, subjects remained under supervision for an additional 5hrs, and on the high dose day each subject was examined by a physician before being released.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">The results were analyzed by means of a 4x5 analysis of variance conducted on the raw score data. The factors were the four time intervals and five drug levels.</td></tr>
<tr><td rowspan="6">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">8.6</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td></tr>
<tr><td>N</td><td>NR</td><td>NR</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>NR</td></tr>
<tr><td rowspan="2">High Quality</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>NR</td><td>Y</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Reaction times and error rates. The preliminary evaluation of reaction time revealed no reliable differences between medium and high dose treatments. Consequently, the medium and high dose days were combined in the final results.</td></tr>
<tr><td>Results</td><td colspan="14">Reaction times: For reaction times on correct responses no significant difference was found between the effects of our medium and high doses of secobarbital, but both differed from a placebo.
Secobarbital had a significant effect on correct reaction times, p <0.001, which amounted to a 208 msec increase in reaction time for the combined drug days relative to placebo.
There was a significant first order drug x visual degradation interaction effect, p <0.05, which reflects a larger drug effect on reaction time when stimulus as degraded by mask. This effect is illustrated in Table 1 with error rate shown in parentheses. All other first order interactions effects involving drug treatment were nonsignificant as follows: drug x character difficulty, F (1.17) = 1.96, p >0.05, drug x rotation (F = 0.17), and drug reversal (F= 1.03). These essentially additive effects are illustrated in Table G-25, Table G-26, Table G-27, and Table G-28.
Error rates: In all conditions, error rates increased with reaction time and did not change significantly across conditions. The differences in error rates produced by each of these variables were in the same direction as the differences in reaction times.</td></tr>
</table>

Authors' Comments	*The results indicate significant increases in the effect of secobarbital on reaction times and errors under conditions of visual stimulus degradation*. The effects of the drug, however, were not changed by 180 degree rotation of the target character or by the other task variables. The results were interpreted to indicate that secobarbital impairs performances primarily by placing selective stress on hypothetical early encoding activities and that later processing operations are not affected by the drug.

Table G-25. Mean Reaction Time and % Error as a Function of Drug Treatment and Stimulus Quality

Stimulus quality	Drug treatment	
	Placebo	Secobarbital
Intact	764 (3.2)	800 (3.4)
Degraded	1200 (6.5)	1481 (9.4)

Table G-26. Mean Reaction Time and % Error as a Function of Drug Treatment and Letter Difficulty

Letter difficulty	Drug treatment	
	Placebo	Secobarbital
Easy (FPR)	824 (2.0)	1008 (2.5)
Difficult (GLJ)	1140 (7.7)	1373 (10.3)

Table G-27. Mean Reaction Time and % Error as a Function of Drug Treatment and Angle of Orientation

Orientation	Drug treatment	
	Placebo	Secobarbital
Upright	844 (2.2)	1046 (4.6)
180 degree rotated	1120 (7.5)	1335 (8.2)

Table G-28. Mean Reaction Time and % Error as a Function of Drug Treatment and Mirror-Image Reversal

Reversal condition	Drug treatment	
	Placebo	Secobarbital
Normal letter	945 (4.2)	1141 (7.3)
Mirror-image	1019 (5.5)	1239 (5.4)

<table>
<tr><td colspan="15">Malpas A, Rowan AJ, Boyce CR, Scott DF. Persistent behavioral and electroencephalographic changes after single doses of nitrazepam and amylobarbitone sodium. Br Med J 1970 Jun. 27; 2(712):762-4.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td colspan="6"></td></tr>
<tr><td></td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="6"></td></tr>
<tr><td>Research Question</td><td colspan="14">To examine the effects of nitrazepam, amylobarbitone and placebo in normal healthy young people</td></tr>
<tr><td>Drug examined</td><td colspan="14">Barbiturates – Amylobarbitone Sodium (Amytal Sodium) 100 and 200 mg, oral</td></tr>
<tr><td>Study Design</td><td colspan="14">Randomized, double-blind, crossover trial in which 10 healthy male volunteers received nitrazepam, amylobarbitone and placebo.</td></tr>
<tr><td rowspan="4">Population</td><td colspan="2">Inclusion Criteria</td><td colspan="12">Age = 18 to 20 yrs. Heathy male volunteer medical students.</td></tr>
<tr><td colspan="2">Exclusion Criteria</td><td colspan="12">NR</td></tr>
<tr><td colspan="2">Study population characteristics</td><td colspan="12">Ten heathy male volunteer medical students aged 18 to 20 years and weighing 69 to 84 kg.</td></tr>
<tr><td colspan="2">Generalizability to CMV drivers</td><td colspan="12">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="14">Each subjects was tested 5 times at 14-day intervals, and on each occasion received orally nitrazepam (5 or 10 mg), amylobarbitone sodium (100 or 200mg), or placebo double-blind according to a Latin square design. Two 5 by 5 Latin squares ensured that each treatment was preceded twice by every other treatment. Sequences of treatment were allotted randomly to the subjects and were dispensed by one of us, who had no contact with subjects; the other three carried out tests.
To reduce the likelihood of undesirable effects and other possible sources of variation, subjects were instructed not to drink any tea, coffee, alcohol, or other depressants or stimulant beverage from 8 p.m. on the experimental night until testing was completed. Each subject was given the appropriate treatment during the day before the experiment. He was instructed to take the pills at 11p.m. the same night and then go to bed. On waking in the morning he filled in a questionnaire about the night's sleep and came to the laboratory a few hours later for testing.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">The behavioral test results were submitted to parametric analysis of variance. Differences between the effects of treatments on the subjective assessments and E.E.G. ratings were analyzed by Friedman's two-way analysis of variance.</td></tr>
<tr><td rowspan="6">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">8.6</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td></tr>
<tr><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>N</td></tr>
<tr><td rowspan="2">High Quality</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>N</td><td>Y</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14"><u>Sleep questionnaire</u>: This was derived from that used by Morgan, Scott, and Joyce (1970) and contained questions relating to the quality, duration, rapidity of onset, and subjective depth of sleep and to condition on awakening. The subjects rated his answer to each question on a 5-point scale such that the middle category represents the "as usual" condition and the highest score indicated maximal hypnotic effect.
<u>Subjective mood scale</u>: (81-item list of adjectives used by Reynolds, Joyce, Tooley, and Weatherall 1965) The subjects rated his answer to each question, as it related to him at the moment , on a 3-point scale- "true", "don't know", "false". In scoring this test, clusters of adjectives relating to tension, good mood, and drowsiness were extracted from the list and the number of times the adjective was in each cluster were checked as true, don't know, or false was totalled for each category.
<u>Card sorting</u>: The time taken to sort 32 playing –cards into 2, 4 or 8 piles was measured in seconds. (Crossman 1953). The total time taken to sort the cards was measured. By subtracting the appropriate motor time from the total time an estimate was obtained of the decision time taken to choose between 2, 4, or 8 responses.
<u>Electroencephalogram (EEG):</u> The first 20 minutes of each record was divided into 10-eonds epochs. Each epoch was independently rated blind by two of us. For the occurrence of electric phenomena associated drowsiness and light sleep. The method of rating was based on that used by Prior and Deacon (1969), a numerical value from 0 to 3 being given to each epoch. The figures obtained were summed to give a total score for each record. The individual ratings were compared at the end of the study and disagreements were resolved.</td></tr>
<tr><td>Results</td><td colspan="14"><u>Sleep questionnaire:</u> Subject did not report hangover effects (drowsiness in waking in the morning) after any of the treatment, and these did not differ in their effects on the subjective onset of sleep. They did rate themselves as having had a better and longer night's sleep after high doses of both drugs than after placebo ($p < 0.05$) or after the lower drug doses.
<u>Subjective mood rating:</u> There were no differences between treatments with respect to feeling of "tension" or "good mood" at either 13 or 17 hours. Subjects rated themselves as "alert" more often after the drug than after placebo ($p < 0.05$) at 13 hours, but this effect was no longer detectable at 17 hours.
<u>Card sorting</u> (Table G-29): Motor performance after placebo was little affected by the number of piles into which the cards were sorted. Neither doses of amylobarbitone slowed performance significantly in comparison with placebo at either time of testing.
Decision time was significantly slowed 13 hours after treatment with 200 mg of amylobarbitone compared with placebo, but 100mg of amylobarbitone resulted in performance significantly slower than placebo for sorting into eight categories only. At 17 hours, some slowing of performance after drug treatment was still apparent, but no difference was statistically significant.
<u>EEG studies</u> (Table G-30): The mean total sleep ratings for each treatment are shown in table III. The scores were higher after each</td></tr>
</table>

	drug treatment than after placebo. The onset of sleep was faster with all drug treatment than with placebo. Ratings of fast activity were higher for all drug treatments.
Authors' Comments	Though they reported a good night's sleep and adjusted to themselves to be alert after all four drug treatments, behavioral tests showed their performance to be significantly impaired 13 hours after treatment with nitrazepam or amylobarbitone, and E.E.G. records showed more drowsiness and light sleep 18 hours after treatment with nitrazepam than with amylobarbitone or placebo. E.E.G. fast activity was more plentiful after drug s in either dosage than placebo.

Table G-29. Time Taken to Sort 32 Cards 13 Hours after Treatment

	Placebo	Nitrazepam		Amylobarbitone	
		5 mg	10 mg	100 mg	200 mg
		Motor Time			
Pile					
2	15 44 - 0 84	15 71 - 0 80	16 25 - 0 82	15 61 - 0 81	15 36 - 0 82
4	15 46 - 0 80	15 78 - 0 80	16 28 - 0 82	15 67 - 0 79	15 63 - 0 81
8	15 61 - 0 79	16 06 - 0 20	16 79 - 0 89	15 90 - 0 81	15 64 - 0 81
		Decision Time			
Categories					
2	14 75 - 2 43	14 97 - 2 12	15 75 - 2 27	14 09 - 2 60	15 49 - 2 09
4	19 94 - 3 14	20 17 - 3 17	20 44 - 3 45	19 70 - 3 75	20 91 - 3 96
8	24 86 - 3 12	25 07 - 4 31	26 70 - 6 05	25 52 - 5 13	26 46 - 4 89

Table G-30. EEG Changes 18 Hours after Treatment

	E.E.G. Sleep Rating (Total Score over 20 Minutes)	Time to Onset of Sleep (Minutes)
Placebo	132 9	10·1
5 mg. nitrazepam	160 2	6·5*
10 mg. nitrazepam	186 2*	5·3*
100 mg. amylobarbitone	149 4	8·5
200 mg. amylobarbitone	150 9	7 8

*Differs from placebo value P = 0 05.

<table>
<tr><td colspan="15">Mills KC, Spruill SE, Kanne RW, Zhang Y. The influence of stimulants, sedatives, and fatigue on tunnel vision: Risk factors for driving and piloting. Hum Factors 2001 SUMMER;43(2):310-27. 9 (Study 1)</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td></tr>
<tr><td></td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="14">To examine the influence of stimulants and sedatives on single-target and divided-attention responses in different parts of the visual field.</td></tr>
<tr><td>Drug examined</td><td colspan="14">Stimulant – Dextroamphetamine 10mg, oral</td></tr>
<tr><td>Study Design</td><td colspan="14">Three-period, placebo-controlled, double-blind crossover in which each volunteer received each of the following treatments: a single 0.5mg dose of alprazolam (Xanax), a single 10 mg dose of dextroamphetamine (Dexedrine), and a single dose of placebo.</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Age = 19 to 37 yrs. All participants consumed fewer than two alcoholic drinks and 500 mg of caffeine per day. None of the participants used alprazolam, dextroamphetamine, nicotine, or illicit drugs in the 30 days prior to the study.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">Volunteers who had taken benzodiazepine or any other prescription drug that had a narcotic, depressant, or stimulant effect within 21 days of study Day 1 were excluded.</td></tr>
<tr><td>Study population characteristics</td><td colspan="13">Variable — Values
n — 18
Age: (yrs.) average (range) — 29.9 (19-37)
Ethnic origins
Caucasians — 14 (77.8%)
African Americans — 4 (22.8%)
Gender M/F — 4 (22.8%) / 14 (77.8%)
Caffeine intake — 44 to 1,861 mg / week</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="14">Volunteers were recruited trough local newspaper advertisements.
On Day 1 participants underwent three POL training sessions. Treatment was administered on Day 2 following overnight housing in the clinic and an overnight fast. The order in which each volunteer received the treatment was randomized, and treatments were separated from each other by three-day washout periods. Drug administration procedures were double-blind: neither the clinic staff nor the participants knew the nature of the drug treatments. Each treatment was accompanied by a series of blood draws over 12 hr for kinetic sampling(Blood samples for the determination of alprazolam and dextroamphetamine plasma concentration were obtained on Day 2 at predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 hr postdose)
The participants completed two subjective rating scales and POL test within 2 min. of each blood draw.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">The scores were analyzed by analysis of variance (ANOVA) for crossover designs in which the variances were partitioned into sequence, participant within sequence, period, treatment effect, and residual error. Testing time relative to dosing was also added to the model to characterize effects over time as repeated measures. To minimize learning effects, all scores were adjusted for baseline differences within each treatment period, creating change-from-baseline scores. No other covariates were added to the model. A probability (p) less than or equal to 0.5 determined statistical significance. Results of the repeated measures ANOVAs for the divide-attention and COMP scores are presented in Table 1</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Internal Validity</td><td colspan="14">Items met (Insert Instrument name and refer to relevant Appendix)</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>8.5</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td></tr>
<tr><td>N</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>NR</td></tr>
<tr><td rowspan="2">High Quality</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>NR</td><td>Y</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">A. Performance online or POL task: measured target-identification and divided- attention responses at three discrete stimulus rings extending outward from the center of a computer display. A divided- attention display occurred when the participants had to respond to both central and outer stimuli; it made up 33% of all displays. The task assessed tunneling by comparing baseline and postdose responses with targets at the three levels of eccentricity
The test was administered with on-screen instructions that ensured participants knew how to respond to each type of display before testing began.
In total, eight scores were collected from POL:
1. Ce – speed and accuracy of space bar response to the central display.
2. Peripheral scores: P1, P2, P3 – speed and accuracy of single responses to stimuli at three rings of the outer display (no divided-attention requirement).
3. Divided-attention scores: D1, D2, D3 – speed and accuracy of divided-attention responses (central and peripheral) to critical stimuli at three increasing visual angles from the central display.</td></tr>
</table>

	4. Composite score: COMP = Ce + P1 + P2 + P3 + D1 + D2 + D3- a single linear combination of all measures. B. **Subjective assessments**: immediately before each POL test, paper-and pencil questionnaires assessed *the participants' perception of sedative and stimulants drug effects*. Seven items comprised the sedative subscale: difficulty concentrating, down, heavy head, inactive, sedated, slow thoughts, and sluggish. Seven items comprised the stimulants subscale: elated, energized, excited, stimulated, talkative, up, and vigorous. Participants circled categories from 0 to 10, with not at all as the lower anchor and extremely as the upper anchor. All the subjective ratings could be completed in less than 1 min. THE Stanford Sleepiness Scale (SSS) was used to assess participants' sleepiness levels. The SSS consisted of seven statements on 7-point scales describing a continuum of sleepiness ranging from feeling active and vital, alert, wide awake to almost in reverie, sleep onset soon, lost struggle to remain awake. The SSS took about 20 s to complete.
Results	**POL:** Significant enhanced performance over the entire field of view was not observed with the dextroamphetamine. *Although the stimulant produced improvements in divided-attention scores and reaction times for the secondary task stimuli near the center of the display, improvement were not observed at the outer limits* of the 44.5 cm diagonal monitors. *In fact, dextroamphetamine produced a linear, inverse relationship between divided-attention performance (and RT) and the distance of the stimuli from the center of the screen.* Tunneling was observed only with divided-attention displays. (Table G-31) **Subjective assessments**: *Significant increased subjective ratings were observed immediately after the 10 mg dextroamphetamine administration (15 min), reaching a peak at 45 min postdose, then gradually dissipating as the plasma levels peaked over the next 2 hr.*
Authors' Comments	Alprazolam impairs performance, whereas dextroamphetamine induces enhancement and tunnel vision.

Table G-31. Results from RM-ANOVAs of Baseline-Adjusted Composite and Divided Attention Scores

		D1		D2		D3		Composite	
Source	*df*	*F* Value	*p* Value	*F* Value	*p* Value	*F* Value	*p* Value	*F* Value	*p* Value
Sequence	2	0.20	0.8208	0.52	0.6046	0.15	0.8628	0.93	0.4169
Subject within sequence error mean squares [a]	15	0.333		0.248		0.207		1.911	
Period	2	9.75	0.0001	2.39	0.0920	6.79	0.0012	9.86	0.0001
Treat	2	5.48	0.0044	20.02	0.0001	12.00	0.0001	31.74	0.0001
Means:									
Alprazolam		0.16 a[b]		–0.52 a		–0.30 a		–1.61 a	
Dexedrine		0.55 b		0.39 b		0.84 b		0.98 b	
Placebo		0.09 a		–0.12 c		0.30 b		0.28 c	
Time	13	1.03	0.4217	1.35	0.1787	1.05	0.3980	2.75	0.0008
Time × Sequence	26	0.78	0.7767	0.60	0.9447	0.77	0.7862	0.57	0.9605
Time × Period	26	0.81	0.7420	0.56	0.9647	0.71	0.8579	0.59	0.9483
Time × Treat	26	0.61	0.9347	1.06	0.3874	0.97	0.5039	1.70	0.0167
Residual error mean squares	696	2.902		2.779		2.091		14.628	

Note: [a] Error Mean Squares represent the model residual and the subject with sequence variability. [b] Treatments with the same letter are not significantly different ($p > 0.05$) within the column.

Moulin DE, Iezzi A, Amireh R, Sharpe WK, Boyd D, Merskey H. Randomised trial of oral morphine for chronic non-cancer pain. Lancet 1996 Jan 20; 347(8995):143-7.

Key Questions Addressed	1	2	3	4	5	6	7	8
		X						

Research Question: Is cognitive function of chronic pain patients affected when placed on opioids?

Drug examined: Opioids – Morphine sustained release oral preparation in doses up to 120 mg daily

Study Design: Randomized, double-blind, two-period crossover study involving a three-week titration phase, a six-week evaluation phase, and a two-week washout to avoid withdrawal symptoms.
Patients completed a high sensitivity cognitive screen pre and post placement on chronic opioids treatment. Control group also used.

Population

Inclusion Criteria: Age= 18-70 yrs. Stable non-cancer pain of at least six months duration treated with morphine sustained release preparation (MS Contin , Purdue Frederick, Pickering, Ontario); average pain over the previous week of at least moderate intensity on a categorical scale and on a visual analogue scale (VSA 0-10 cm); regional pain of a myofascial, musculoskeletal, or rheumatic nature; failure to respond to non-steroidal anti-inflammatory drugs and at least one tricyclic antidepressant (TCA) known to be analgesic in this patient population. (response failure to a TCA defined as minimum dose of 25 mg maintained for at least one month without significant benefit); and effective birth control for women of childbearing age. Informed consent.

Exclusion Criteria: History of drug or ethanol abuse; history of psychosis or a major depressive syndrome; neuropathic pain syndromes including reflex sympathetic dystrophia; isolate headache syndromes (tension –type, migraine, or mixed headaches); presence of congestive heart failure or history of myocardial infraction in the past year; history of an allergic reaction to morphine or codeine; history of asthma, epilepsy, or hepatic or renal (serum creatinine greater than 150µmol/L) disease. Patients with isolated headache syndromes were excluded because of the possible complicating feature of analgesic rebound. Patients were excluded if they had previously used a major opioids analgesic such as oxycodone, morphine, or hydromorphone for their chronic pain. A history of codeine treatment was allowed, because most Canadian patients with chronic pain have had a trial of codeine. - it is available over the counter as an 8 mg tablet combined with either paracetamol (acetaminophen) or aspirin and is often prescribed by family physician at higher doses.

Study population characteristics (of 61 patients at study entry)

	Mean	Median	Range	%
Age	40.4	40	26-67	
Sex: M/F			41/ 59	
Married				64
Education(yr)	12.9	13	8-19	
Employed				25
Litigation				28
Injury related pain				85
Duration of pain(yr)	4.1	3.4	0.75-21	
	Mean	Median	Range	%
Codeine history				
Daily dose (mg)*	126.5	120	0-360	
Duration (mo.)	32.2	24	0-156	
TCA history†				
Daily dose (mg)	43.9	25	25-150	
Duration (mo)	9.3	4	1-72	
Local anesthetic or Steroid injection				46
Non pharmacological treatments				
Physiotherapy				93
TENS – acupuncture				77
Psychotherapy				39
Surgery				21
Symptom Check List-90‡	68.3	68.0	47-81	
Profile of Mood States § High Intensity Cognitive Screen §	4.1	94.5	41-184	
	50.6	49.0	14-115	
Sickness Impact Profile ¶	24.0	22.6	4.7-54.6	
Physical dimension	17.2	15.0	0-44.9	
Psychosocial dimension	25.3	24.0	0- 84.2	
Pain Disability Index	44.1	45.0	14-65	

* Averaged over previous week in 60 patients ; † use of tricyclic antidepressants known to be analgesic(most common amitryptiline) ; † overall score(Global Severity Index) from30 to 81 with higher values indicating greater impairment; § overall scores with higher values indicating greater impairment (Profile of Mood States scores from 0-260, High Sensitivity Cognitive Screen 0-249); ¶ overall scores with higher values indicating worse function (Sickness Impact Profile scored 0-100, Pain Disability Index 0-70)

<table>
<tr><td></td><td>Generalizability to CMV drivers</td><td colspan="14">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="15">Morphine was administered as a sustained- release preparation in weekly graded doses of 15.30, and 60 mg tablets twice daily during the titration phase with maintenance of the highest tolerated dose during the evaluation phase. Benztropine (PMS Benztropine, Pharmascience, Montreal, Quebec) was used as the active placebo in weekly graded doses of 0-25, 0-5, and 1-0 mg capsules twice daily in similar fashion. Benztropine has no analgesic properties but mimics many of the possible side-effects of morphine, including sedation, lightheadedness, nausea, dry mouth, constipation, and urinary hesitancy. Matching placebos were used to blind the treatment in each period of the study. The washout phase consisted of decreasing doses of drug in reverse order to the titration phase with maintenance at the lowest level of study medication during the second week of washout. Patients then crossed over to the opposite treatment arm for identical titration, evaluation, and washout phases. Titration phase = 3 weeks, evaluation phase = 6 weeks, and washout phase = 2 weeks. Patients were seen weekly during the titration and washout phases and every two weeks during the evaluation phase.</td></tr>
<tr><td>Statistical Methods</td><td colspan="15">The sample size calculated was based on VAS (1-10 cm) for pain intensity, which was designated as the primary outcome measure. A sample size of 42 was determined to be sufficient to detect a difference of 1cm with a standard deviation of 2cm to provide 90% power at the 0.05 significance level. Analysis of variance (ANOVA) was used to test for sequence (carryover), drug, and time effects (SAS, Cary, NC). When no evidence of differential carryover was found (p >0.10) the data from both periods were used to examine the overall treatment difference and difference at each time of testing. In the case of differential carryover ANOVA was performed on data from the first period only. All p values for pain indices reflect analysis of titration and evaluation phases. McNemar's chi-square test was used to compare the frequency of side effects with morphine and placebo and ANOVA was used to compare the duration x severity scores for major side-effects.</td></tr>
<tr><td rowspan="6">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>NR</td><td>NR</td><td>NR</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>N</td><td>Y</td><td>NR</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">6.0</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td></tr>
<tr><td>N</td><td>Y</td><td>Y</td><td>NR</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>N</td><td>Y</td><td>N</td><td>Y</td><td>NR</td></tr>
<tr><td rowspan="2">Moderate Quality</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>NR</td><td>Y</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="15">Pain intensity, pain relief, and drug liking were rated weekly and psychological features, functional status, and cognition were assessed at baseline and at the end of each evaluation phase.
1. Baseline levels of pain were assessed with VAS for pain intensity averaged over the previous week and the McGill Pain Questionnaire (primary outcome measure).
2. Subtle cognitive changes were assessed by means of the High Sensitivity Cognitive Screen (included measures of memory, language, attention, and planning).
3. Psychological features including anxiety and depression were assessed by use of Symptom Check List-90(SCL-90) and Profile of Mood States (POMS).
4. Quality- of- life issues were examined with the Sickness Impact Profile and the Pain Disability Index.</td></tr>
<tr><td>Results</td><td colspan="15">103 patients met all of the predetermined inclusion criteria and were considered for study participation. 42 declined to participate or were not otherwise suitable- 15 were fearful of morphine addiction, or pain during the placebo phase, 10 had transportation problems, 8 simply did not want to take part in a "research experiment", 5 had conflicts with their full-time work, and 4 were not sufficiently fluent in English.
Study sample: 15 patients dropped out because of inadequate pain relief, unacceptable side –effects, (Table G- 33) or both and were lost to follow-up. 11 dropped out during morphine titration and 4 during placebo titration (p = 0.008, chi-square). The study dropouts were compared with completers according to demographics, clinical characteristics, and various subscales of the Symptom Check List-90 and Sickness Impact Profile and there were no significant differences except for ambulation on the Sickness Impact Profile where completers had a higher score (p = 0.05, student's t-test). The remaining 46 patients were included in the analysis; 43 completed both six-week evaluation phases.
20 patients were titrated up to the highest dose of morphine (60 mg twice daily), 22 reached the middle dose (30md twice daily), and 4 tolerated the lowest dose (15 mg twice daily). The mean daily dose of morphine was 83.4 (SD 33.0) mg. 32 patients were able to tolerate the highest dose of active placebo (1mg twice daily) and 14 were maintained on the middle dose (0-5 mg twice daily). The mean daily dose of active placebo was 1.7 mg (0-5) mg.
Pain intensity: The mean scores for Total Pain Rating Index, for all subscales of the McGill Pain Questionnaire, and for pain relief (VAS) showed no significant treatment, carryover, or period effects.
On visual analogue scales, the morphine group showed a reduction in pain intensity relative to placebo in period I (p = 0.01) and this group fared better in a crossover analysis of the sum of pain intensity differences from baseline (p = 0.02). No other significant differences were detected.
When morphine and placebo were compared in terms of the sum of pain intensity differences from baseline (VAS) in each treatment period, there was a greater reduction with morphine (p = 0.02) without carryover or period effects. However, the actual weekly mean pain intensity scores showed a sequence effect (p = 0.02) with a possible differential carryover from period I treatment to period II. The comparison for mean pain intensity was therefore based on first period data alone and this also showed a morphine treatment effect (p = 0.01).
Psychological and functional outcomes at end of evaluation phase (Table G-32) The overall scores showed no significant differences or changes from baseline measures.
No differences were found between study periods on a cognitive screening test that included measures of memory, language, attention, and planning.</td></tr>
</table>

Authors' Comments	In patients with treatment-resistant chronic regional pain of soft tissue or musculoskeletal origin, nine weeks of oral morphine in doses up to 120 mg daily may confer analgesic benefit with a low risk of addiction but is unlikely to yield psychological or functional improvement.

Table G-32. Psychological and functional outcomes at end on evaluation phase

Scores	Morphine (n=46)	Placebo (n= 46)	Differences* (95% CI)
Symptoms Check List-90 (Total Score)	67.7	67.7	0-0 (-1.9,1.9)
Somatisation	71.1	70.3	0.8 (-1.3,2.8)
Depression	67.1	66.9	0.2 (-2.0,2.5)
Anxiety	62.8	63.2	-0.4 (-3.5,2.6
Hostility	60.9	57.9	**3.0 (0.1,5.9)**
Profile of Mood States	99.6	103.2	-3.6 (-13..6,6.4)
High Sensitivity Cognitive Screen (Total Score)	41.4	45.0	-3.6 (-8.3,1.0)
Memory	25.1	28.3	**-3.2 (-6.1,-0.1)**
Language	7.0	7.3	-0.3 (-2.2,1.7)
Attention and concentration	3.6	3.5	0.1 (-0.8, 1.0)
Self planning and regulation	3.2	3.7	-0.5 (-2.0,1.0)
Sickness Impact Profile† (Total Score)	24.5	24.2	0.3 (-2.0,2.5)
Physical dimension	16.4	15.4	1.0 (-1.2, 3.4)
Psychological dimension	26.5	28.1	-1.6 (-5.6,2.4)
Pain Disability Index	44.6	45.0	-0.4 (-2.8,2.0)

None of the differences statistically significant except hostility subscale of Symptom Check List-90 (p = 0.04) and memory subscale of High Sensitivity Cognitive Screen (p = 0.04); † only most relevant subscales of Symptom Check List-90 and sickness Impact Profile are shown (overall score for Symptom Check List-90 is the Global Severity Index).

Table G- 33. Common side-effects of morphine and active placebo (benztropine) in 46 patients

Side effects	Morphine %	Placebo%	Both%	P*=
Vomiting	39	2	4	0.0002
Dizziness	27	2	13	0.0004
Constipation	41	4	15	0.0005
Poor appetite /nausea	39	7	41	0.002
Abdominal pain	22	4	7	0.04
Fatigue	22	7	11	0.10
Dry skin / itching	15	4	7	0.18
Dry mouth	17	11	24	0.58
Diarrhea	13	13	11	0.77
Blurred vision	13	20	13	0.61
Sleeplessness	13	17	11	0.79
Confusion	9	15	4	0.55
Dose- limiting side effects†	28	2	28	0.003

* Difference in side-effect frequency according to McNemar's chi-square analysis; † values indicating percentage of patients who did not reach the maximum dose because of side-effects.

<table>
<tr><td colspan="11">Pishkin V, Lovallo WR, Fishkin SM, Shurley JT. Residual effects of temazepam and other hypnotic compounds on cognitive function. J Clin Psychiatry 1980; 41(10):358-63.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td colspan="3">8</td></tr>
<tr><td></td><td>X</td><td></td><td></td><td></td><td></td><td></td><td colspan="3"></td></tr>
<tr><td>Research Question</td><td colspan="10">To examine the effects of single dose of temazepam and other commonly prescribed hypnotic compounds on several behavioral and cognitive tasks.</td></tr>
<tr><td>Drug examined</td><td colspan="10">Barbiturates – (Equal parts of sodium secobarbital and sodium amobarbital) - 200mg, oral</td></tr>
<tr><td>Study Design</td><td colspan="10">Five group design, controlled study in which the effects of temazepam were compared to those of flurazepam, barbiturate and placebo.</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="9">Age = 21 to 30yrs. Male subjects enrolled as students at the University of Oklahoma Health Science Center. Subjects found normal at physical examination and who had values on blood chemistry, blood cell count, differential and urinalysis measures that were within 15% of normal. Informed consent.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="9">Subjects who require any concomitant medications during the period of the study, and subjects with known hypersensitivity to drugs with a chemical structure similar to temazepam, such as flurazepam, diazepam, chlordiazepoxide or oxazepam, or to barbiturates. Also eliminated were subjects who during the period of four weeks prior to study initiation received any other investigational drug and those who within the past three months had received any drug known to have a well-defined potential of toxicity. Subjects who had any disease or symptoms of acute or chronic clinical illness in the four weeks preceding the study were also excluded, as well as those with known cardiovascular disorders. Subjects who had received any minor tranquilizers, daytime sedative or nighttime hypnotic within the 3-day period immediately prior to initiation of active study medication were not tested. Those who had a history of alcoholism, drug abuse, or addiction were also excluded. Subjects were excluded who had any disease or abnormal conditions which compromised the function of the following systems: gastrointestinal tract, liver and kidneys.</td></tr>
<tr><td>Study population characteristics</td><td colspan="9">Fifty males aged 21 to 30. Subjects weighted between 63.5 and 86.2 kg or within 15% of their normal weight as determined by Metropolitan Life Insurance Company norm.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="9"></td></tr>
<tr><td>Procedures</td><td colspan="10">Subjects volunteered in response to an ad placed on bulletin board s at the school of medicine. On the day of drug or placebo treatment, each subject had his vital signs measured and was given preliminary familiarization with the simple reaction time and pursuit rotor tasks and was administered the Shipley Hartford Scale as a measure of general intelligence. The subject was given his coded bottle containing nothing, placebo, or drug, and *was instructed to take the content, if any, within a half-hour of his normal bedtime* and to refrain from caffeine or alcohol following dinner. The following morning the subject entered the laboratory at 9:00a.m., ad his vital signs were taken. He then completed the simple reaction time, pursuit rotor, and speeded inference tasks. He was questioned as to adverse reactions, debriefed, and release.
Fifty coded bottles were used, each containing one capsule of either 30 mg temazepam, 30 mg flurazepam, 200mg barbiturate (Equal parts of sodium secobarbital and sodium amobarbital), a placebo (lactose), or the bottle was empty.
The experiment included five groups: temazepam, flurazepam, barbiturate, a placebo control and no capsule.</td></tr>
<tr><td>Statistical Methods</td><td colspan="10">The simple reaction time and pursuit rotor results allowed a predrug versus postdrug comparison after drug administration. Speeded inference data were collected only postdrug and thus permitted only comparison between groups at that one time. (See *Results*)
Data relating to adverse reactions and vital signs are being analyzed for publications elsewhere.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>Yes</td><td>NR</td><td>NR</td><td>No*</td><td>NR</td><td>Yes</td><td>NR</td></tr>
<tr><td rowspan="2">4.2
Low Quality</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>Yes</td><td>Yes</td><td>Yes</td><td>No*</td><td>No*</td><td>Yes</td><td>No</td><td>Yes</td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="10">Each subjects was tested on three performance tasks: A test of reaction speed, a test of sensory-motor ability (pursuit rotor), and a rest of decision making speed(speeded inference) with two levels of difficulty (++ and --)
1. **Simple reaction time**: This task was administered the afternoon prior to drug administration and the morning after. The test was conducted by having the subject view a blank ground glass screen and watch for the occurrence of a brief light. Upon the presentation of the light, the subject responded as rapidly as possible by speaking the non-sense word “TAT” into a microphone connected to voice operated relay which activated a printer that automatically recorded the reaction time in milliseconds.
2. **Pursuit rotor:** Requires tracking a moving target, measures eye-hand coordination. This task was administered the afternoon prior to drug administration and the morning after.
3. **Speeded inference**: Measures speed at which the subjects could make relatively complex decisions as to the presence or absence of physical characteristics on successive stimuli. The task was divided in half, the first half being concerned with the detection of the similarity between successive stimuli (++ condition), and the second half with the absence of an attribute from two successive stimuli (-- condition).This task was only presented following drug administration.</td></tr>
<tr><td>Results</td><td colspan="10">As an appropriate means of checking the groups with respect to intelligence level, the Shipley Hartford test was administered and each subject’s mental age derived. A one-way analysis of variance revealed that there were no differences among the 5 groups (F = .18, df = 4/45, NS). Likewise, there were no statistically significant differences between the three drug groups reporting adverse reaction utilizing a standard phase III check list (chi-square = 4.59, df = 3, P >.05)
Pursuit rotor (Table G-34): The results suggest a tendency for the temazepam group to produce morning-after performance superior</td></tr>
</table>

	to those of the barbiturate group. All groups improved from predrug to postdrug tests, indicating a practice effect (P <0.001).The temazepam group improved the most from predrug to postdrug. A one-way analysis of covariance was run on the postdrug data, using predrug performance as covariate. As a result, the corrected time-on-target shows the temazepam group with numerically the best performance of any group and the barbiturate group with the worst. Overall, however the group effect was not significant, and a comparison of temazepam and barbiturate groups revealed only a slight trend toward significantly better performance (P = .123). **Simple Reaction Time (**Table G-35): The results suggest a tendency for subjects to show superior performance the morning after receiving a dose of temazepam compared to subjects taking a dose of barbiturate. All groups improved from predrug to post drug tests, (P <.0005) although the temazepam group improved the most (.038 sec), and the barbiturate group improved the least (0.015 sec). As with pursuit rotor data, these scores were subjected to an analysis of covariance in which the groups postdrug performances were compared, corrected for their predrug performances. The groups were not significantly different in simple reaction time (P <.25), but comparison between groups showed the temazepam group to be significantly faster in reaction time that the barbiturate group (P <.05). **Speeded Inference Task (**Table G-36**,** Table G-37**):** The groups did not differ in the speed at which they could make relatively complex decisions as to the presence or absence of physical characteristics on successive stimuli. However the placebo and temazepam subjects made more errors on speeded inference (--conditions) than those receiving no compound and markedly fewer than those receiving flurazepam and barbiturate. Thus, these latter compounds apparently impaired the accuracy of timed decision making by the subjects in these groups, although this impairment was less for those taking temazepam.
Authors' Comments	Results showed a slight superiority for temazepam over barbiturate on visual motor and reaction time tasks. On one phase of a cognitive task, the barbiturate and flurazepam groups made more errors than the control groups. *Overall, the results indicate impairment in performance for the group taking barbiturate* and a smaller impairment for the flurazepam group. No detectable impairment occurred for subjects taking temazepam.

Table G-34. Pursuit Rotor, Mean Time on Target for Five Fifteen-Second Trials

Drug Condition	Predrug	Postdrug	Postdrug Corrected for Predrug
No Compound	7.03	9.60	9.63
Placebo	8.30	10.39	9.36
Temazepam	6.12	9.31	10.09
Barbiturate	6.42	8.67	9.21

Values of t and Probability Levels for Pairwise Comparisons of Adjusted Postdrug Means

Comparisons Between Drug Conditions	t	P
Placebo vs Temazepam	1.221	0.229
Placebo vs Flurazepam	0.198	0.844
Placebo vs Barbiturate	0.265	0.792
Temazepam vs Barbiturate	1.571	0.123

Table G-35. Simple Visual Reaction Times in Seconds

Drug Condition	Predrug	Postdrug	Postdrug Corrected for Predrug
No Compound	0.462	0.436	0.436
Placebo	0.475	0.456	0.446
Temazepam	0.458	0.420	0.422
Flurazepam	0.450	0.428	0.436
Barbiturate	0.463	0.428	0.448

Values of t and Probability Levels for Pairwise Comparisons of Adjusted Postdrug Means

Comparisons Between Drug Conditions	t	P
Placebo vs Temazepam	1.889	0.065
Placebo vs Flurazepam	0.758	0.452
Placebo vs Barbiturate	0.174	0.863
Temazepam vs Barbiturate	2.071	0.044

Table G-36. Speeded Inference + + Condition, Means of Median Reaction Times

Drug Condition	Postdrug	Postdrug Corrected for Predrug
No Compound	0.627	0.627
Placebo	0.654	0.646
Temazepam	0.658	0.659
Flurazepam	0.654	0.660
Barbiturate	0.612	0.611

Values of t and Probability Levels for Pairwise Comparisons of Adjusted Postdrug Means

Comparisons Between Drug Conditions	t	P
Placebo vs Temazepam	0.296	0.759
Placebo vs Flurazepam	0.312	0.756
Placebo vs Barbiturate	0.767	0.447
Temazepam vs Barbiturate	1.065	0.293

Table G-37. Speeded Inference - - Condition, Means of Median Reaction Times

Means of Median Reaction Times

Drug Condition	Postdrug	Postdrug Corrected for Predrug
No Compound	0.907	0.907
Placebo	0.888	0.878
Temazepam	0.938	0.941
Flurazepam	0.954	0.963
Barbiturate	0.927	0.926

Values of t and Probability Levels for Pairwise Comparisons of Adjusted Postdrug Means

Comparisons Between Drug Conditions	t	P
Placebo vs Temazepam	0.927	0.359
Placebo vs Flurazepam	1.240	0.221
Placebo vs Barbiturate	0.713	0.479
Temazepam vs Barbiturate	0.216	0.830

<table>
<tr><td colspan="15">Redpath JB, Pleuvry BJ. Double-blind comparison of the respiratory and sedative effects of codeine phosphate and (+/-)-glaucine phosphate in human volunteers. Br J Clin Pharmacol 1982 Oct; 14(4):555-8.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td></tr>
<tr><td></td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="14">To compare the respiratory effects of glaucine phosphate and codeine phosphate in volunteers with regard to both intensity and duration of effect. (Glaucine phosphate is used in eastern Europe as an antitussive agent).</td></tr>
<tr><td>Drug examined</td><td colspan="14">Opioids – Codeine phosphate 30 mg and 60 mg (syrup)</td></tr>
<tr><td>Study Design</td><td colspan="14">Double-blind, crossover trial in which ten healthy volunteers received codeine phosphate, glaucine phosphate or placebo</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Age = 23 to 36 yrs. Healthy volunteers. Free from chronic respiratory, cardiovascular or psychiatric diseases. Had not taken medication (with the exception of oral contraceptives) for 14 days preceding the trial. The three smokers were asked to refrain from smoking for the whole trial day and the subjects were also asked to refrain from alcohol for the 12 h preceding the trial.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">NR</td></tr>
<tr><td>Study population characteristics</td><td colspan="13">Ten healthy volunteers (four female). Age = 23 to 36 yrs. (mean 26 yrs.)
Weight = 50-75 kg (mean 64kg)</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="14">Glaucine phosphate 30 mg and 60 mg, codeine phosphate 30 mg or 60 mg and placebo were prepared in 10 ml of identical syrup vehicles. The drugs were assigned to he subjects on a double-blind crossover design. The sequence of administration was arranged on the basis of two 5x5 Latin squares. All tests were carried out prior to drug administration and ventilatory measurements were repeated 0.5, 1.5, 2.5, 3.5, and 6 h after administration of the syrup. Pulse, blood pressure and psychological tests were performed 1, 2, 3, 4, and 6 h after the syrup had been taken.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Significance was assessed using Duncan's multiple range test.</td></tr>
<tr><td rowspan="6">Quality assessment</td><td rowspan="2">Internal Validity</td><td colspan="13">Items met (Insert Instrument name and refer to relevant Appendix)</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">8.8</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td></tr>
<tr><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>NR</td></tr>
<tr><td rowspan="2">High Quality</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>NR</td><td>Y</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">1.Ventilation and ventilatory response to CO2
2.Pulse and blood pressure
3.Sedation was measured using a visual analogue 100 mm scale marked at one end 'Wide awake' and at the other end 'Nearly asleep'
4.Cognitive function was tested using the digit symbol substitution test (DSST)(Wechsler, 1944).
5.Time taken to assimilate information was assessed using the Zahlen-Verbindung Test. Twenty-four numbers were arranged randomly in a circle and they had to be connected in ascending order. The time taken for completion of this task was recorded.</td></tr>
<tr><td>Results</td><td colspan="14">Both glaucine phospate 60 mg and codeine phosphate 30 mg caused significant displacement of the ventilatory response to carbon dioxide at 201 min. (Table G-38). There were no significant differences in slope change between treatments and there were no significant differences between respiratory parameters breathing air after the five treatments. Pulse and blood pressure were not affected by any of the treatments and neither was performance in the Zahlen-Verbindung.
However, sedation scores were significantly increased by 60mg glaucine at 60 min post drug.(Table G-39) The sedative effect of 60 mg glaucine was coupled with a decreased performance at 60 min in the digit symbol substitution test (P <0.05). Performance was reduced by 4.5 ±2.0 symbols in 90s by 60 mg glaucine while the same subjects given placebo increased their performance by 0.7 ±1.1 symbols in 90 s.
Codeine phospate had no detectable sedative activity.</td></tr>
<tr><td>Authors' Comments</td><td colspan="14">Both the codeine and glaucine phospate displaced the ventilatory response to carbon dioxide to the right.
The effect of codeine on the ventilatory response to carbon dioxide was not dose dependent: 30 mg produced greater effects than 60 mg dose. Only the highest dose of glaucine phosphate (60mg) caused respiratory depression and this was associated with sedation and decreased performance in the digit symbol substitution test. Neither antitussive agent had significant effects upon pulse or blood pressure and codeine phosphate had no detectable sedative activity.</td></tr>
</table>

Table G-38. Effect of Glaucine Phosphate and Codeine Phosphate on Displacement (kPa) of the Ventilatory Reponse to Carbon Dioxide

Treatment	Pre-drug	Change from pre-drug records at 20 l minute volume: 30 min	90 min	150 min	210 min	360 min
Glaucine 30 mg	6.27 ± 0.20	+0.23 ± 0.17	+0.22 ± 0.17	+0.10 ± 0.08	−0.03 ± 0.19	+0.06 ± 0.12
Codeine 30 mg	6.16 ± 0.22	+0.39 ± 0.18	+0.62 ± 0.23*	+0.55 ± 0.24*	+0.40 ± 0.24	+0.76 ± 0.29
Codeine 60 mg	6.51 ± 0.43	+0.19 ± 0.26	+0.21 ± 0.19	+0.29 ± 0.13	+0.04 ± 0.28	+0.18 ± 0.34
Glaucine 60 mg	6.39 ± 0.31	+0.53 ± 0.21	+0.80 ± 0.22*	+0.63 ± 0.20*	+0.40 ± 0.16	+0.54 ± 0.17
Placebo	6.70 ± 0.45	−0.17 ± 0.26	−0.20 ± 0.28	−0.08 ± 0.23	−0.21 ± 0.18	−0.01 ± 0.25
F value		1.44	3.09	2.55	1.58	1.81
Significance between treatments		NS	$P < 0.05$	$0.1 > P > 0.05$	NS	NS

*Significant change from placebo values ($P < 0.05$)

Table G-39. Effect of Glaucine Phosphate and Codeine Phosphate on Sedation Score

Table 2 Effect of (±)-glaucine phosphate and codeine phosphate on sedation score

Treatment	Pre-drug	Change from pre-drug score (mm on 100 mm visual analogue scale): 60 min	120 min	180 min	240 min	360 min
Glaucine 30 mg	12.9 ± 3.2	+13.7 ± 5.0	+15.7 ± 8.1	+4.9 ± 4.8	+2.9 ± 4.4	+5.7 ± 7.0
Codeine 30 mg	14.7 ± 5.7	+2.9 ± 3.4	+6.9 ± 8.5	−1.2 ± 4.4	−4.3 ± 2.1	+2.6 ± 3.4
Codeine 60 mg	18.4 ± 7.5	+1.7 ± 2.2	−4.2 ± 5.8	−5.8 ± 5.1	−9.9 ± 6.5	−8.9 ± 7.0
Glaucine 60 mg	17.1 ± 7.9	+20.0 ± 7.6*	+15.1 ± 9.0	+4.3 ± 8.3	−3.9 ± 7.1	−4.8 ± 9.3
Placebo	14.2 ± 3.8	+1.1 ± 2.9	+2.3 ± 4.4	−1.3 ± 2.9	−3.0 ± 2.2	+2.8 ± 4.7
F value		3.38	1.31	0.68	0.84	0.84
Significance between treatments		$P < 0.05$	NS	NS	NS	NS

*Significant change from placebo ($P < 0.05$)

<table>
<tr><td colspan="15">Saarialho-Kere U, Mattila MJ, Seppala T. Pentazocine and codeine: effects on human performance and mood and interactions with diazepam. Med Biol 1986; 64(5):293-9.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td></tr>
<tr><td></td><td>X</td><td></td><td></td><td></td><td></td><td></td><td>X</td></tr>
<tr><td>Research Question</td><td colspan="14">To study the interactions between narcotics and diazepam as well as to compare the effects of pentazocine and codeine alone on objective and subjective estimates of performance</td></tr>
<tr><td>Drug examined</td><td colspan="14">Opioids – Codeine 100mg (oral)</td></tr>
<tr><td>Study Design</td><td colspan="14">Double-blind, crossover</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Healthy students</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">NR</td></tr>
<tr><td>Study population characteristics</td><td colspan="13">10 healthy students volunteers (5 males and 5 females) aged 20-26 years and weighing 58-77kg
The students were social drinkers and none of them regularly used medicines</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="14">The subjects with no previous experience of any benzodiazepine were given 10 mg diazepam two weeks before the first session. This was done to reduce the development of behavioral tolerance to diazepam during the experimental period.
The subjects received double-blind and crossover single doses of placebo, pentazocine (75mg) and codeine (100 mg as codeine phosphate) at two weeks intervals. The treatments were randomized according to Latin Square. The tests were done 1h 30 min, 3 h, 4 h and 4h 30min after the initial drug intake. Diazepam (0.25 mg/kg) was given immediately after the test at 1h 30min. For safety, naloxone was given intravenously after the 4 h test to eliminate possible late effects of opiates.
The tests were always given in the same order.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Mean ±SEM values were computed from the raw data separately for the absolute test performances as well as for Δ-values (changes from baseline). The latter represents responses to drugs and they were compared against respective placebo values (paired t –test; Wilcoxon test). Since the treatment sequences may modify performances and drug responses. A split-split plot ANOVA was computed for drug responses using mean variance as wall as its contributions by the subject, test week, test time, drug and their mutual relation as variables. Side –effects scored on the questionnaire were analyzed with Fisher's exact probability test.</td></tr>
<tr><td rowspan="6">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">9.0</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td></tr>
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<tr><td>N</td><td>Y</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Objective tests: Digit Symbol Substitution, Flicker Fusion, Body Sway on an electronic platform, Maddox Wing test , and the measurement of lateral gaze nystagmus
Subjective effects were measured on visual analogue scales (VAS): the subjects locate their position on a horizontal 100mm ungraded line between the two extremes. The two extremes were drowsy/alert; calm/nervous; mentally slow/quick witted; hostile/friendly; sad/happy; bored/interested; discontent/content; silent/talkative; very bad performance/very good performance; lazy/effective; withdrawn/social.
The subjects also scored various psychosomatic symptoms from 0 to 3 on a 42-item questionnaire
(VIGFIN) which was filled after every test-time. Blood pressure and heart rate were measured at baseline and at 3h.</td></tr>
<tr><td>Results</td><td colspan="14">Obvious learning effects was seen in the baselines of digit symbol substitution test which improved from the first to the third week (P <0.001; paired <i>t</i> test). The baseline values for the angle nystagmus showed an opposite trend, showing an impairment (decrease) with weeks (P <0.05). On the other hand, the baseline values in all VAS- assessment remained similar.
<i>Pentazocine and codeine alone failed to modify performance in objective tests. With regard to subjective assessments codeine tended to slow the subjects mental responses (P <0.005; t test).</i>
<u>Combined effects of analgesic and diazepam (Table E-1)</u>: These effects can be seen from the results recorded at the 3h, 4h and 4 h 30min tests. Neither codeine nor pentazocine added significantly to the diazepam induced impairment in objective tests. When given after codeine the peak effects of diazepam on scales drowsy/alert (P <0.05, Wilcoxon test) and calm / nervous (P <0.05) appeared later than after placebo + diazepam. <i>Codeine counteracted diazepam induced feeling of impaired performance (Wilcoxon test; P <0.05</i>). Neither diazepam nor the opiates modified the variable satiated / hungry; there was a general trend towards feeling more hungry as the time passed.
<u>Side-effects</u>: The subjects reported side-effects such as headache, blurred vision, dry mouth, nausea, vomiting, itching, drowsiness, increased perspiration and dizziness similarly when on placebo or analgesics. This was due to the relatively strong effects of diazepam present in each group. The trend of diazepam to lower systolic blood pressure reached statistical significance when given after pentazocine and codeine (t-test; P <0.01 vs. baseline). Diastolic blood pressure and heart rate remained uninfluenced by the treatments.
<u>Pharmacokinetics</u>: The plasma concentration of the analgesics and diazepam are given in Table G-41.
It appears that the concentrations of analgesics were low in morphine equivalents, Codeine yielded bioassayed concentrations which</td></tr>
</table>

	are comparable to those after 10 mg oral dose of morphine. When analgesics were given before diazepam the plasma diazepam levels did not peak so strongly at 3h. When analyzing the chemically assayed diazepam concentrations with two-way ANOVA (treatment x time), a significant (P <0.01) difference was found between treatments (placebo, pentazocine, codeine) but not between times. This was mainly attributable to lowered diazepam concentrations after codeine. When the same diazepam was analyzed with paired-t-test, the concentration ratio 90 min/ 3h was not significantly altered by analgesics. The latter also applies to bioassayed diazepam concentrations. Accordingly, *lowered plasma diazepam concentrations after codeine can reflect reduced rather than postponed absorption of diazepam.*
Authors' Comments	*Codeine and pentazocine alone failed to affect performance in objective tests* (body sway, digit symbol substitution, flicker fusion, Maddox wing, and nystagmus) recorded at 1h 30min. Visual analogue scale showed subjective drug effects: codeine made the volunteers mentally slow. 75mg of pentazocine and 100mg of codeine produced comparable plasma opiate activity (determined in morphine equivalents) according to radioreceptor bioassay. Impaired performance was clear at the tests done 1.5 and 2.5 h after diazepam. No major interactions were found between opiates and diazepam in objective tests with the exception that nystagmus was stronger after the combined treatments than after diazepam alone. Codeine reduced the absorption of diazepam. *Subjectively codeine and pentazocine counteract the effects of diazepam*. *The subjects overestimated their performance after opiates + diazepam when compared to diazepam alone.* The results suggest that no major harmful interactions on performance take place when moderate oral doses of opiates and benzodiazepines are given in combination. The lack of impairment of performance by codeine and pentazocine in the present trial disagrees with previous results obtained with intramuscular pethidine. The route of administration obviously contributes much to the effects of narcotic analgesics on performance since only occasionally have oral doses been reported as affecting psychomotor skills. In contrast to objective data, subjective parameters were affected by narcotic analgesics in the present trial. Both narcotics tended to counteract the effect of diazepam on subjective performance. *Diazepam alone gave the subjects the realistic feeling of affected capability while the opiates seemed to upset this view*. This fact could turn out to be potentially dangerous in practical situations. *The effects of codeine were sen in VAS scale bad performance / good performance*. As a mu-agonist codeine particularly, is suggested as having a prominent euphoric action.

Table G-40. Absolute scores for some tests (mean +/- SEM)

Test/Group	Baseline	1.5 h*	3 h**	4 h***	4.5 h
Digits substituted					
Placebo	157 ± 8	153 ± 7	138 ± 7[c]	138 ± 8[b]	140 ± 6[c]
Pentazocine	148 ± 6	148 ± 6	131 ± 7[b]	128 ± 6[c]	134 ± 6[b]
Codeine	156 ± 6	151 ± 6	133 ± 9[c]	133 ± 8[c]	138 ± 7[b]
Maddox wing (d)					
Placebo	−4.9 ± 1.0	−5.0 ± 1.1	−6.8 ± 1.1[a]	−7.1 ± 1.1[a]	−6.5 ± 1.1
Pentazocine	−4.3 ± 0.9	−4.5 ± 0.7	−7.1 ± 1.1[c]	−7.3 ± 1.1[c]	−7.4 ± 1.2[c]
Codeine	−4.3 ± 1.1	−4.9 ± 1.1	−6.5 ± 1.3[a]	−6.8 ± 1.3[b]	−6.5 ± 1.2[b]
Drowsy/alert (mmVAS)					
Placebo	49 ± 7	39 ± 5	29 ± 6[a]	27 ± 5[a]	38 ± 3
Pentazocine	54 ± 6	52 ± 5	41 ± 4	30 ± 5[a]	40 ± 4
Codeine	48 ± 6	43 ± 6	30 ± 4[a]	28 ± 3[a]	40 ± 3
Bad/good performance (mmVAS)					
Placebo	57 ± 6	45 ± 5[a]	29 ± 5[b]	27 ± 4[c]	37 ± 6[a]
Pentazocine	53 ± 5	48 ± 3	33 ± 4[b]	35 ± 4[b, d]	37 ± 5[b]
Codeine	47 ± 4	41 ± 3	31 ± 4[b, d]	33 ± 3[b, d]	41 ± 3

* diazepam was given at 1 h 45 min; ** second dose of pentazocine was given at 3 h 15 min; *** naloxone was injected at 4 h 15 min. a = $P < 0.05$, b = $P < 0.01$, c = $P < 0.001$ vs. baseline, paired *t*-test. d = $P < 0.05$ vs. placebo, paired *t*-test.

Table G-41. Mean Plasma Levels of Analgesics and Diazepine

Treatment/ Time	Analgesics ng/ml		Benzodiazepines ng/ml	
	Bioassay	GLC	Bioassay	GLC
Pentazocine				
1 h 30 min	6±2	12±4		
3 h	7±2	25±4	481±92	405±56
4 h 30 min	19±5	39±6	565±109	369±44
Codeine				
1 h 30 min	6±1	105±2		
3 h	6±1	93±10	412±72	334±68
4 h 30 min	7±2	78±8	434±112	318±51
Placebo				
3 h			598±95	526±111
4 h 30 min			527±61	382±95

Given are means ± SEM. Bioassayed concentrations of analgesics refer to ng/ml of standard morphine and bioassayed plasma benzodiazepine (diazepam + metabolites) concentrations refer to ng/ml of standard diazepam. Plasma nordiazepam levels were low (5—30 ng/ml) according to gas-liquid-chromatography (GLC).

Sabatowski R, Schwalen S, Rettig K, Herberg KW, Kasper SM, Radbruch L. Driving ability under long-term treatment with transdermal fentanyl. J Pain Symptom Manage 2003 Jan; 25(1):38-47.

Key Questions Addressed	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
		X		X					

Research Question

To examine the effects of long- term treatment with transdermal fentanyl on complex psychomotor and cognitive performance measures that are thought to be related to driving ability.

Drug examined

Opioids – Transdermal fentanyl

Study Design

Non-randomized controlled trial design: Individuals with chronic non-cancer pain receiving stable doses of transdermal fentanyl compared to healthy age and sex matched controls (Fentanyl to control ratio = 1:3)

Study was designed as a non-inferiority trial.

Population

Inclusion Criteria

Fentanyl group: Age = 18 to 65 yrs. Outpatients suffering from chronic non-cancer pain responsive to opioids. Treated with transdermal fentanyl for at least 4 weeks without dosage change in the previous 12 days. Valid driving license. Ability to speak and write in German. Informed consent.

Control group: Age = 18 to 65 yrs. Controls randomly selected from pool of volunteers. Control sample described as representative of the normal German population with regard to activity, autonomy, and driving experience.

Exclusion Criteria

Fentanyl group: Treated with the following drugs: benzodiazepines of barbiturates >3 times per week; high doses of antidepressant (e.g., ≥75mg amitriptyline per day); antihistamines. Physical disabilities, severe psychiatric or neurological disease, or visual disorder that would prevent performance of study tests.

Control group: Treated with drugs that may affect test performance. Physical disabilities, severe psychiatric or neurological disease, or visual disorder that would prevent performance of study tests.

Study Population Characteristics

	Fentanyl group	Control group
n	30	90
Age: (yrs) mean ±SD (range)	50 ±9 (34-65)	50 ±9 (34-65)
Sex: % male	18(60%)	57(63%)
Diagnosis:		
Lower back pain	18	–
Neuropathic pain syndromes	6	–
Miscellaneous	6	–
Duration of pain (months): median (range)	36 (2–216)	–
Pain intensity(NRS) : mean ±SD	3 (0–8)	–
Driving experience (km/yr): median (range)	10,000 (500–60,000)	–
Driving license (years) : median (range)	27 (5–46)	–
Time on fentanyl	At least 4 weeks	0
Plasma fentanyl concentration at the time of testing: median (range)	1.35 ng/ml (0.53-17.7)	0

Generalizability to CMV drivers

Unclear

Procedures

Testing was performed one week after the screening. Prior to testing, a blood sample was taken to determine the plasma fentanyl concentration, and a urine sample was taken to screen for the use of drugs not reported by the patients. The entire test battery takes about 75 minutes to perform, with the vigilance test at the end taking 25 minutes.

Statistical Methods

Mann-Whitney U-test. A one-sided P-value <0.05 was regarded as significant.

Delta (δ) defined as deficit in test observed when blood alcohol >0.05%.

The sample size needed to demonstrate non-inferiority using 1:1 randomization was calculated as 39 (one-sided t-test, $\alpha = 0.05$, $\beta = 0.20$), assuming no difference between patients, and controls. In order to reduce the required number of patients, Investigators decided to perform a 1:3 randomization, namely, three controls were matched to each patient. This gave a sample size of 26 patients and 78 controls. Investigators therefore aimed to enroll 30 patients to allow for dropouts or protocol violators.

Quality assessment

Internal Validity	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
	No*	No*	Yes	Yes	No*	NR	Yes	Yes	Yes	No*	NR	No*	No*

4.2 Low Quality	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	
	No*	No*	No*	No*	Yes	Yes	Yes	No*	No*	Yes	No	Yes	

Relevant Outcomes Assessed

Tests designed to evaluate driving ability(in Germany):

1. Attention test (**COG**)
2. Test for reaction time under pressure, determination test (**DT**)

	3. Test of visual orientation, tachistoscopic perception (**TAVT**) 4. Test for motor coordination (**2-Hand**) 5. Vigilance test (**VIG**) The primary endpoint was defined as the sum of the scores of the DT, COG, and TAVT tests after z-transformation of the individual scores, using the mean and the standard deviation of the whole sample. Urine screening detected use of unreported drugs such as cocaine, morphine, thebaine, benzodiazepines and antidepressants in 9 cases (in fentanyl group). Data from these patients were included in the **intent-to-treat (ITT**) analysis, while the remaining 21 patients without violation of the study protocol were analyzed as the **per-protocol (PP)** group.
Results Q2	**Sum Score (**Table G-42**)** (Primary Endpoint): For the sum of the z-transformed DT, COG and TAVT-scores, representing the cognitive items of the test battery, significant non-inferiority could be shown for the PP-group in comparison to the control group (0.22 ±2.30 versus -0.05 ±2.57, P = 0.036), but not for the ITT-group (0.06 ±2.21 versus -0.20 ±2.58, P = 0.38). **COG (**Table G-43**)**: The number of correct answer and mean reaction time were similar in the fentanyl and control groups. Both of the fentanyl groups (ITT, PP) were statistically non-inferior to the control + δ group (P <0.05) in this respect. However the ITT group gave more wrong responses. Therefore, although the calculated score of the PP-group proved to significantly non-inferior (P = 0.037) to the control + δ group, the ITT- group did not. **DT (**Table G-43**):** The number of correct answers was the lowest in the ITT-group and significant non- inferiority could only be shown for the PP group (P = 0.034). Mean reaction time was marginally longer in the ITT-group than in the PP-group and in the control group. Significant non-inferiority could only be shown for the PP-group (P = 0.015) but not for the ITT-group (P = 0.3). **TAVT (**Table G-43**)**: The mean number of mistakes was almost the same in all three group and significant non-inferiority could be shown in both analyses (ITT: P = 0.004; PP: P = 0.003). **2-Hand (**Table G-43**)**: The mean time for passing the track was longer (i.e., worst) in the ITT-group, followed by the PP-group and the control group. For the PP-group, significant non-inferiority to the control group could be shown (P = 0.029).The percentage of time off the track was lowest in the ITT-group, followed by the PP-group and the control group. Thus, significant non-inferiority could be shown in both analyses (P <0.001 for ITT and PP). For the calculated score, significant non-inferiority cloud be demonstrated for the PP-group (P = 0.019) but not for the ITT-group (P = 0.1). **VIG (**Table G-43**)**: The mean number of mistakes was lowest in the PP-group, followed by the control group and the ITT-group. Almost no difference was observed for the mean time to a correct response (MRT) between the three groups. Significant non-inferiority in comparison to the control group was shown in both analyses (ITT, PP) for both parameters, as well as for the calculated scores (all P values <0.005). **Passed Tests**: Percentage of patients who passed the single tests (i.e., scored above the 16th percentile): The results of the PP-group, as well as of the ITT-group, demonstrated no statistically significant difference from the control group in any of the five tests. If one considers all three primary target tests (DT, COG and TAVT) simultaneously, it was found that all three were passed by 60% of the patient in ITT-group and by 67% of patients in the PP-group, as compared to 74% of the patients in the control group. There was no statistically significant difference in the number of tests failed between the fentanyl groups and the control (P = 0.224). There was no correlation between driving experience (kilometers per year) or current pain intensity and the different items of the test battery. However, the age of the patient correlated with the number of 'processed items' of the DT (P = 0.001), the number of 'correct answers' of the DT (P <0.001), as well as the sum score of the DT (P <0.001), of the TAVT (P = 0.002) and the relevant score after z- transformation (P <0.001).
Authors' Comments	*Results from this study demonstrated that the performance of the patients receiving long-term treatment with transdermal fentanyl was significantly non-inferior to that of the control group*. Patients suffering from chronic non-cancer pain who are treated with a stable dose of transdermal fentanyl do not have a clinically significant impairment of psychomotor or cognitive function which would prevent them from performing complex daily activities, such as driving a car. The results also suggested that the additional intake of illicit drugs can compromise test results. Several variables that might have an impact on performance such as the etiology of the pain and the use of a historical control group for comparison have not been evaluated

Table G-42. Sum Score of the z-transformed DT, COG, and TAVT

Variable	Fentanyl group ITT	Fentanyl group PP	Control group (raw values)	Control group (raw values + δ)
Size (n)	30	90	21	90
Sum Score	0.60 (2.21)	-0.20 (2.58)	0.22 (2.30)	-0.05 (2.57)

Results are presented as arithmetic mean (SD)
Results shown to be significantly non-inferior compared to the control group (P >0.05)
n.a. = data not available
The results of the control group are presented as raw values as well as the calculated result of the effect of impairment due to alcohol (raw value transformed by δ and the variance of the item in the whole sample)

Table G-43. Psychomotor and cognitive performance measures including the calculated score of the different tests.

Variable	Fentanyl group ITT	Fentanyl group PP	Control group (raw values)	Control group (raw values + δ)
COG (n)	30	21	90	90
Wrong answers (n)	34.23 (17.92)*	28.98 (16.28)*	26.83 (14.29)	35.69 (14.29)
Correct answers (n)	53.03 (11.09)*	53.62 (11.89)*	53.70 (10.29)	47.74 (10.29)
MRT(sec)	1.08 (0.10)*	1.10 (0.09)*	1.01 (0.07)	1.15 (0.07)
Score	9.09 (1.01)	8.86 (1.08)*	8.36 (1.36)	9.36 (1.36)
DT(n)	30	21	90	90
Processed items(n)	438.8 (73.79)	459.1 (72.67)	n.a.	n.a.
Wrong reactions (n)	19.93 (12.91)	19.71 (14.23)	n.a.	n.a.
Correct reactions (n)	418.87 (72.9)	439.38 (70.75)*	443.70 (72.07)	402.22 (72.07)
MRT (sec)/score	1.18 (0.210	1.12 (0.19)	1.11(0.20)	1.23 (0.20)
TAVT(n)	30	21	90	90
Processing time (sec)	267.7 (108.22)	252.81 (81.16)	n.a.	n.a.
Wrong answers (n)/score	30.53 (13.11)*	29.76 (15.31)*	29.08 (14.74)	37.23 (14.74)
2-HAND (n)	30	20	90	90
Mean time (sec)	42.97 (14.75)	37.54 (11.82)*	36.35 (14.29)	44.68 (14.29)
Time off rack (%)	4.429 (3.85)*	5.09 (4.42)*	5.26 (4.32)	7.66 (4.32)
Score	6.12 (2.31)	5.65 (2.26)*	5.38 (2.18)	6.64 (2.18)
VIG (n)	29	20	90	90
Wrong answers (n)	7.34 (10.01)*	5.85 (6.62)*	6.88 (6.78)	11.24 (6.78)
MRT (sec)	0.52 (0.08)*	0.51 (0.09)*	0.52 (0.07)	0.56 (0.07)
Score	2.20 (1.24)*	2.01 (1.13)*	2.23 (0.97)	2.81 (0.97)

Results are presented as arithmetic mean (SD)

*Results shown to be significantly non-inferior compared to the control group (P >0.05)

n.a. = data not available

The results of the control group are presented as raw values as well as the calculated result of the effect of impairment due to alcohol (raw value transformed by δ and the variance of the item in the whole sample)

Silber BY, Papafotiou K, Croft RJ, Ogden E, Swann P, Stough C. The effects of dexamphetamine on simulated driving performance. Psychopharmacology (Berl) 2005 May;179(3):536-43.

Key Questions Addressed	1	2	3	4	5	6	7	8
		X						

Research Question: To examine the acute effects of 0.42 mg / kg dexamphetamine on simulated driving performance, and to establish which, if any, simulated driving abilities become impaired following dexamphetamine administration.

Drug examined: Stimulants: Dexamphetamine, 0.42 mg/ kg, oral

Study Design: Repeated measures, counter-balanced, double-blind, placebo-controlled, crossover trial in which subjects received dexamphetamine and placebo.

Population

Inclusion Criteria: Age = 21 to 32 yrs. Valid, full driver's license (no probationary, or learner drivers) to ensure that they had at least 3 years of driving experience. Informed consent. No history of substance abuse; no pre-existing physical or neurological conditions; no history of psychiatric, cardiac, endocrine, gastrointestinal or bleeding disorders; not pregnant or lactating; not taking nay prescription medication (except the contraceptive pills); not regular amphetamine users (i.e., they used less than once a month). Only participants who had previously experienced with amphetamines were permitted to participate. All participants consented to refrain from consuming alcohol for 24 h and no illicit drugs for at least 7 days prior to each session.

Exclusion Criteria: NR

Study population characteristics

Variable	Values
n	20
Age: (yrs.) mean ±SD	25.4 ±3.3
Average male weight (kg):	82.1 ±10.6
Average female weight (kg):	62.2 ±10.4
Number of years of education(minimum)	11
Gender M/F	10/10

Generalizability to CMV drivers: Unclear

Procedures

Twenty healthy participants were recruited through advertisements.

Participants completed two treatment conditions: placebo tablet and dexamphetamine tablet. *Participants completed the two sessions 1 week apart to reduce traces and any cumulative effects of the drug if it was consumed during the first session.*

In preliminary session, on a day in which no drug was administered, participants completed the four simulated driving tasks. Upon arrival on the two experimental days, participants completed the city-traffic simulated driving task (to refamiliarize themselves with the driving simulator). The research nurse then administered the treatment. As dexamphetamine has a peak blood concentration of between 120 min and 180 min, the first blood and saliva samples were obtained 120 min after drug administration, followed by the Snellen Eye Test and the driving simulator tasks. The second set of blood and saliva samples were then obtained (170 min post drug administration).

Statistical Methods

As the driving simulator task required participants to drive in city and freeway scenarios in two simulated conditions (day and night), dat were analyzed separately for day- (freeway and city combined) and night- (freeway and city combined) driving tasks. For each of the day and night conditions, a test of difference in proportions based on paired data was performed to establish whether there was nay relationship between overall simulated driving ability and the presence of dexamphetamine, where the independent variable was drug condition (placebo vs. dexamphetamine) and the classification of driving ability (impaired vs. not impaired) was the dependent variable. A Bonferroni adjustment was made to correct for type-1 error resulting in a corrected alpha level of 0.025.

The second set of analyses was a series of Wilcoxon signed- rank tests. These explored the effects of dexamphetamine on each individual driving simulator variable, where drug condition (placebo vs. dexamphetamine) was the independent variable and the score for each driving variable was the dependent variable. No corrections for multiple comparisons were made, as theses analyses were exploratory.

Two paired samples-*t*-test were performed to determine whether dexamphetamine affected visual acuity. A Pearson's correlation was performed to determine whether any dexamphetamine- related changes in simulated driving performance were associated with changes in visual acuity.

Quality assessment

Items met (Insert Instrument name and refer to relevant Appendix)

Internal Validity	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
	Y	NR	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
8.2	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	NR
High Quality	**27**	**28**											
	NR	NR											

Relevant Outcomes Assessed: The driving simulator was a CyberCAR LITE driver training and evaluation simulator. Participants observed a two-dimensional computer generated driving scene, as they would through a vehicle windscreen.

	The driving module consisted of four tasks- "freeway traffic driving" and "city traffic driving", under both day and night conditions. Each task took approximately 5 min to complete. The computer program record each driver's performance continuously on a range of variables, in terms of vehicle management and conformance to the pre-programmed set of driver and vehicle standard operating procedures. A subset of 34 relevant variables was analyzed, where each reflected an error that can occur during the driving tasks. All adjusted variable scores were summed to give an overall impairment score. Driving simulator variable scores were summed separately for the day and night conditions. For each, a total score between 0 and 75 was classified as "not impaired" on the driving simulator task, whereas a total score of 76 and above constituted an assessment of :impaired" on the driving task. The Snellen Eye Chart is a standard measure of visual acuity (higher score indicated better vision). This was administered to clarify whether any dexamphetamine–related change in performance were associated with changes in visual acuity. Blood and saliva samples: Blood and saliva samples were obtained prior to the driving tasks and immediately after task completion (120 min and 170 min post-drug administration respectively).
Results	Blood and saliva samples: The mean dexamphetamine concentration levels in blood and saliva at 120 min after drug administration were 83 ng/ml and 236 ng/ml, respectively, and at 170 min after drug administartion98 ng/ml and 242 ng/ml, respectively. The Snellen Eye Chart: *Visual acuity in the left eye significantly decreased under the dexamphetamine condition (P = 0.04)*; however there was no difference of acuity in the right eye when comparing the dexamphetamine and placebo conditions (P = 0.55) Driving simulator: *An overall reduction in simulated driving performance was observed under dexamphetamine condition (19 of 20 participants "impaired") relative to placebo condition (13 of 20 "impaired") for the day-time simulated driving condition (P <0.05, 95% CI = -0.528 to -0.028*).However, dexamphetamine did not affect overall simulated driving ability under the night-time driving condition (dexamphetamine 17 of 20 impaired; placebo 17 of 20 impaired; P >0.05, 95% CI = -0.230 to 0.230). Simulated day driving (city and freeway combined) (Table G-44): There was an overall trend towards decreased signaling adherences under the dexamphetamine condition, such as at intersection (P <0.01),when entering a freeway (P = 0.096) and during lane changes, (P = 0.08). Additionally the was a tend found towards drivers failing to stop at the red traffic light more frequently under the dexamphetamine than placebo condition (P = 0.06). A significant difference was found between the two conditions with regard to the speed the vehicle was travelling on a freeway when an emergency situation occurred, with more drivers under the dexamphetamine condition than placebo condition travelling at o slower speed (P <0.01). Poorer visual acuity in the left eye under the dexamphetamine condition was not found to be associated with the observed decrease in simulated day-time driving performance (P = 0.63) Simulated night driving (city and freeway combined) (Table G-44, Table G-45): There was a trend towards a decrease in reaction time under the dexamphetamine condition (P = 0.07).
Authors' Comments	The results of the present study suggest *that dexamphetamine does decrease simulated driving performance in recreational users in day-time driving scenario*. It is not clear whether it also occurs under night-time driving conditions due to the limitations of the night component of the task. *Contributing to this overall reduction in day-time simulated driving performance, there was some evidence to suggest that dexamphetamine affected signaling and traffic light adherence, and drivers were found to travel significantly more slowly under the simulated freeway condition*. These results are consistent with perceptual narrowing or tunnel vision effects, where peripheral vision is impaired with dexamphetamine; however, this interpretation remains tentative and further research is needed to clarify this issue.

Table G-44. Driving Simulator Results

Driving simulator variables (day)	
Collision	T=30.50, P=0.813
Dangerous action skid	T=0, P=0.157
No signal cancel when entering freeway	T=3, P=0.096
No signal when entering freeway	T=9, P=0.739
Incorrect signalling at intersection	T=0, P=0.004
No signal cancel at intersection	T=0, P=1.000
Wheels not straight on approaching intersection	T=2.5, P=0.317
No signal when changing lane	T=46, P=0.084
No signal cancel when changing lane	T=32, P=0.340
No signal when moving off	T=38.5, P=0.969
No signal cancel when moving off	T=22.5, P=1.000
Waited too long before moving off	T=12, P=0.705
No signal cancel when overtaking (left)	T=6, P=0.680
No signal cancel when overtaking (right)	T=3, P=0.180
No signal when overtaking (left)	T=0, P=0.083
No signal when overtaking (right)	T=5.5, P=0.581
Inappropriate braking	T=60, P=0.675
Driving too fast	T=1.5, P=0.414
No safe following distance	T=57.5, P=0.584
Driving too slow	T=35.5, P=0.773
Straddled barrier line	T=2, P=0.131
Wandering	T=52.5, P=0.414
Wide/cut	T=8, P=0.257
Released brake inappropriately when stopping	T=0, P=0.317
Not sufficient clear space when stopping	T=0, P=0.180
Needless/unnecessary stop	T=11, P=0.305
Did not stop at red traffic light	T=4, P=0.059
Straddled the solid line	T=6, P=0.655
Exceeded speed limit	T=54.5, P=0.750
Advanced situation collision	T=7, P=0.414
Speed of vehicle when emergency situation occurred (freeway)	T=24, P=0.004*
Speed of vehicle when emergency situation occurred (city)	T=68, P=0.167*
Reaction time (emergency stop)	T=71, P=0.334*
Stopping distance from vehicle/object at emergency stop (freeway)	T=31, P=0.177*
Stopping distance from vehicle/object at emergency stop (city)	T=3, P=0.225*
Skidding when stopping during advanced situation	T=57, P=0.858*
Driving simulator variables (night)	
Collision	T=18, P=0.564
Dangerous action skid	T=0, P=0.317
No signal cancel when entering freeway	T=13.5, P=0.480
No signal when entering freeway	T=12, P=0.705
Incorrect signalling at intersection	T=49, P=0.816
No signal cancel at intersection	T=0, P=0.317
Wheels not straight on approaching intersection	T=20, P=0.739
No signal when changing lane	T=59.5, P=0.419
No signal cancel when changing lane	T=48, P=0.295
No signal when moving off	T=34, P=0.234
No signal cancel when moving off	T=27.5, P=1.000
Waited too long before moving off	T=1.5, P=1.000
No signal cancel when overtaking (left)	T=9, P=0.739
No signal cancel when overtaking (right)	T=24.5, P=0.442
No signal when overtaking (left)	T=8, P=0.132
No signal when overtaking (right)	T=7.5, P=0.260
Inappropriate braking	T=47.5, P=0.473

Table G-45. Driving Simulator Results Continued

Driving simulator variables (night)	
Driving too fast	T=2, P=0.129
No safe following distance	T=54.5, P=0.751
Driving too slow	T=50, P=0.868
Straddled barrier line	T=10.5, P=0.527
Wandering	T=28.5, P=0.404
Wide/cut	T=9, P=0.739
Released brake inappropriately when stopping	T=0, P=0.317
Not sufficient clear space when stopping	T=6, P=0.655
Needless/unnecessary stop	T=18.5, P=0.331
Did not stop at red traffic light	T=2, P=0.564
Straddled the solid line	T=2, P=0.257
Exceeded speed limit	T=60.5, P=0.690
Advanced situation collision	T=1.5, P=0.414
Speed of vehicle when emergency situation occurred (freeway)	T=92, P=0.627*
Speed of vehicle when emergency situation occurred (city)	T=84, P=0.433*
Reaction time (emergency stop)	T=44, P=0.071*
Stopping distance from vehicle/object at emergency stop (freeway)	T=17, P=0.155*
Stopping distance from vehicle/object at emergency stop (city)	No results*
Skidding when stopping during advanced situation	T=65.5, P=0.894*

<table>
<tr><td colspan="15">Sjogren P, Olsen AK, Thomsen AB, Dalberg J. Neuropsychological performance in cancer patients: the role of oral opioids, pain and performance status. Pain 2000; 86(3):237-45.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td></tr>
<tr><td></td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="14">To evaluate the possible influence of long-term oral opioids, pain and reduced health status on some aspects of psychomotor function and cognition in cancer patients</td></tr>
<tr><td>Drug examined</td><td colspan="14">Opioids – morphine and others - oral</td></tr>
<tr><td>Study Design</td><td colspan="14">Cross-sectional design (study comparing 5 groups of cancer pain patients)</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Age = 40-76 yrs. Cancer patients. In all five groups only peripherally acting analgesics were allowed.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">Patients taking other psychotropic drugs (benzodiazepines, antidepressants, anti-convulsants, neuroleptics, etc), suffering from metabolic disturbances, in ongoing anti-neoplastic therapy, drinking alcohol beverages or suffering from brain metastases or other neurological and/or physical dysfunctions interfering with the tests.</td></tr>
<tr><td>Study population characteristics</td><td colspan="13">In order to evaluate and separate the influence of performance status, pain and oral medication, 130 patients were allocated in a cross-sectional design to five different groups (Table G-46, Table G-47). The patients in groups 4a and 4b were in regular and stable dose of oral opioid treatment for >2 weeks. All opioid doses are given as milligrams of oral morphine. For opioids other than morphine an equipotency table was used for conversion</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="14">All testing were performed in the following sequence: CRT, FTT and PASAT and lasted approximately 1h.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Non-parametric statistical methods were applied. The Mann-Whitney rank sum test or Kruskal-Wallis test for more than two groups were used for “between groups” analyses (unpaired data). The Wilcoxon signed rank test was used for “within groups” analysis (paired data). Correlations were assessed by means of Spearmen’s rank correlation test (r(s)) and chi-square test was used for contingency tables. All tests were two-tailed and general level of significance was set at P = 0.05. The number of patients included in the study was determined by statistical power calculation from a former study (Banning and Sjogren, 1990) and a statistical evaluation when half of the patients were included.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>NR</td><td>NR</td><td>NR</td><td>Y</td><td>NR</td><td>NR</td><td>Y</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>NR</td></tr>
<tr><td rowspan="2">5.0
Low Quality</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td>N</td><td>N</td><td>N</td><td>N</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>N</td><td>Y</td><td>Y</td><td></td></tr>
<tr><td>Relevant outcomes assessed</td><td colspan="14">1. Pain intensity, sedation, opioid doses, time from ingestion of last opioid dose to testing and opioid side effects. Sedation and pain level were evaluated by the patient using 100 mm visual analogue scales (VAS): sedation (SVAS); pain (PVAS).
2. The neuropsychological tests used were:
a) Continuous reaction time (CRT): measure vigilance, i.e., the ability of the individual to attend to and respond rapidly to external stimuli for an extended period of time. Through headphones, 152 auditory stimuli were delivered to the patient at random interval. The patients were instructed to press a button as soon as they heard the sound. Reaction time was measured in 1/100s.
b) Finger tapping test (FTT): examines the patient’s ability to tap a key as fast as possible. The score for each hand was the average of five trials.
c) Paced auditory serial addition task (PASAT): measures working memory, another aspect of attention. The task reflects the capacity for divided attention and is a measure of information processing speed. The Patient was presented verbally with 61 random digits between 1 and 9 at timed interval and was instructed continually to add the last digit to the previous one. The number of correct answers was counted. Initially the interval between each digit is 2.4 s(T 2.4, then 2.0 s (T 2.0), 1.6 s (T 1.6) and finally 1.2 s (T 1.2).Un fortunately cancer patients find this sensitive test very stressful and difficult, and based on earlier experience with PASAT in cancer patients only the two longest intervals were used (T2.4 and 2.0 respectively)</td></tr>
<tr><td>Results</td><td colspan="14">Comparison between groups: There were no statistically significant differences between any of the groups concerning age and sex distribution at baseline.
Regarding category B (50-70%) of KPS there were no statistically significant differences between these groups. No statistically significant differences between groups 3 and 4a in PVAS were found. In group 4a, SVAS scores and opioid doses were statistically significantly higher than in group 4b (p = 0. 02 and 0.002, respectively). Between these two groups there were no statistically significant differences in time from opioid ingestion to testing.(Table G-48)
CRT: Group 1 was statistically significantly faster than group 2 and 4b in the 90th percentile (p = 0.043 and 0.05, respectively) and than group 4a in both the 50th and 90th percentiles (p = 0.032 and 0.001, respectively).
FTT: Group 1 was statistically significantly faster than group 3 with the dominant hand (DOM) (p = 0.016) and than group 4a with both DOM and non-dominant (NDOM) (p = 0.00004 and 0.0006) respectively.
PASAT: Group 1 performed statistically significantly better than group 4a in T2.4 (p = 0.004).
Group 4b performed statistically significantly better than group 4a in T2.4 (p = 0.007).
In order to gain more information about the possible influence of pain and oral opioid treatment on neuropsychological performance, group 2, 3, 4a and 4b, all being in KPS B were analyzed as follows. The non-opioid treated group 2 and 3 versus the opioid treated</td></tr>
</table>

	groups 4a and 4b did not show statistically significant differences in the three tests, whereas *the pain-relieved groups 2 and 4b versus the pain –suffering groups 3 and 4a showed statistically significantly better performance in PASAT T 2.0 (p = 0.022).* Correlations (Table G-49, Table G-50): Correlation between the three neuropsychological tests was analyzed to evaluate the independence of measures. Table 4 shows statistically significant correlations between CRT and FTT within groups. Correlations between the neuropsychological tests and other variables were analyzed to assess consistency across patients groups. Table 5 shows correlations between the neuropsychological tests and age, sex, KPS, SVAS and opioid-related side effects within the groups. The only side effect that correlated with the tests (CRT and FTT) was drowsiness in group 4b. No statistically significant correlation could be demonstrated between the neuropsychological tests and PVAS, pain types, opioid dose and time from ingestion of opioids to testing. Drop-out analyses: Although the PASAT test was modified by using the two longest intervals (T 2.4 and T 2.0, respectively) only 55% of the patients were able to carryout the test at least at one of the speeds. There were no statistically significant differences between patients participating once (T2.4) or twice (T2.0) in the test regarding age, sex, KPS, SVAS,PVAS, opioid doses and the performance of CRT and FTT. Forty five percent of the patients were not able to participate in PASAT. These patients were not statistically significantly different from the participating patients regarding age, sex, KPS, SVAS, PVAS, opioid doses. However the non-participants patients performed statistically significantly poorer in CRT and FTT (p <0.05)
Authors' Comments	The authors conclude that in cancer patients the impact of stigmatizing factors (oral opioids, pain, and reduced performance status) seem to impair some of important aspects of neuropsychological performance, but more specifically our results indicate that 1) the use of long-term oral opioid treatment in cancer patient per se did not affect any of the neuropsychological tests used in the present study, 2) cancer patients being KPS B had statistically significantly slower CRT than patients being in KPS A and 3) pain itself may deteriorate the performance of PASAT more than oral opioid treatment. Major problems regarding the study design: • The patients in the poorest category of KPS (KPS C) were not participating. Clinical experience and research concurrently indicated that declining health and performance status and increasing frequency and severity of cognitive dysfunctioning are associated. Thus, feasibility reasons omitting category C of KPS important information about patients being "unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly" are lacking • Selection and institutional bias might be present due to the fact that a limited number of departments within the community of Copenhagen participated in the study, which favors the accrual of certain cancer diagnoses. • The role of mood was not taken into account in this study. To our knowledge the relationship between neuropsychological performance and mood has not yet been established in cancer patients, but such relationship is well described in patients with major depressive disorder and in patients with chronic non- malignant pain conditions. • - The use of PASAT in cancer patients may be reconsidered as the large number of drop-out may involve selection bias.

Table G-46. Study Groups Outcome Parameters

Groups[a]	Outcome
1. KPS A, no pain, no opioid medication, $N = 40$	Karnofsky Performance Status
2. KPS B, no pain, no opioid medication, $N = 19$	Pain
3. KPS B, pain, no opioid medication, $N = 19$	Oral opioids
4a. KPS B, pain, opioid medication, $N = 31$	Pain
4b. KPS B, no pain, opioid medication, $N = 21$	

[a] KPS, Karnofsky Performance Status; *N*, number of patients.

Table G-47. Demographic and Clinical Data

Group (*N*)	Age (years)	Sex (F/M)	Cancer diagnoses	KPS	PVAS	SVAS	Pain type
1 (40)	62.5 (49–73)	21/19	Breast, 12; lung, 5; GI, 9; UG, 4; HN, 7; others, 3	90 (80–100)	–	–	
2 (19)	63 (40–75)	4/15	Lung, 6; GI, 2; UG, 2; HN, 8; others, 1	70 (60–70)	–	3 (0–48)	
3 (19)	58 (46–76)	6/13	Lung, 1; GI, 4; UG, 2; HN, 10; others, 2	70 (50–70)	24 (10–93)	8 (0–54)	Neu, 9; Vi, 7; So, 7
4a (31)	59 (47–74)	10/21	Lung, 10; GI, 6; UG, 6; HN, 6; others, 3	60 (50–70)	35 (2–88)	25 (0–90)	Neu, 11; Vi, 3; So, 26
4b (21)	60 (46–73)	9/12	Breast, 4; lung, 7; GI, 3; UG, 1; HN, 4; others, 2	70 (50–80)	–	0 (0–49)	

[a] Age, KPS, PVAS and SVAS are given as medians and ranges. F, female; M, male; PVAS, pain VAS; SVAS, sedation VAS; KPS, Karnofsky Performance Status; GI, gastrointestinal cancer; UG, urogenital cancer; HN, head and neck cancer; Neu, neuropathic pain; So, somatic pain; Vi, visceral pain.

Table G-48. Clinical Data Concerning Opioid Use

Group (*N*)	Opioid doses (mg)	Time from opicid ingestion to testing (min)	Opioid related side effects
4a (31)	120 (25–420)	180 (12–360)	Drowsiness, 17; constipation, 12; nausea, 8; dizziness, 6; pruritus, 4
4b (21)	40 (20–180)	120 (60–420)	Drowsiness, 10; constipation, 10; dry mouth, 10; nausea, 6; pruritus, 4

[a] All opioid doses were converted into morphine using a relevant equipotency table. Data are given as medians and ranges.

Table G-49. Statistically Significant Inter-Test Correlations

Group	Inter-test correlations	Correlating parameter within the tests	*P*-values	*r*-values
1	CRT/FTT	10th DOM/NDOM	0.020	−0.37
2	CRT/FTT	10th DOM/NDOM	0.041/0.022	−0.49/−0.55
		50th DOM/NDOM	0.045/0.019	−0.48/−0.56
		90th NDOM	0.027	−0.54
3	CRT/FTT	10th DOM/NDOM	0.027/0.004	−0.54/−0.66
		50th DOM/NDOM	0.033/0.004	−0.50/−0.66
		90th DOM/NDOM	0.024/0.002	−0.53/−0.69
4b	CRT/FTT	10th DOM/NDOM	0.0001/0.0002	−0.75/−0.73
		50th DOM/NDOM	0.0001/0.0001	−0.77/−0.77
		90th DOM/NDOM	0.0003/0.0001	−0.71/−0.76

[a] CRT, continuous reaction time; 10th, 50th and 90th, percentiles of CRT distributions; FTT, finger tapping test; DOM, dominant hand; NDOM, non dominant hand.

Table G-50. Statistically Significant Correlations Between Neuropsychological Tests and Other Variables

Group	Tests	Age	Sex	KPS	SVAS	Drowsiness
1	CRT 10th		$P = 0.037$			
	CRT 50th		$P = 0.006$			
	CRT 90th		$P = 0.008$			
	FTT (NDOM)	$P = 0.0007$, $r = -0.52$ ($N = 39$)			$P = 0.02$, $r = -0.36$ ($N = 39$)	
	PASAT T 2.4	$P = 0.05$, $r = -0.39$ ($N = 26$)				
	PASAT T 2.0				$P = 0.02$, $r = 0.65$ ($N = 13$)	
2	CRT 90th	$P = 0.02$, $r = 0.53$ ($N = 19$)				
	FTT (DOM)		$P = 0.015$			
	PASAT T 2.4	$P = 0.006$, $r = -0.82$ ($N = 9$)				
3	CRT 10th	$P = 0.03$, $r = 0.51$ ($N = 19$)				
	CRT 50th	$P = 0.009$, $r = 0.58$ ($N = 19$)				
	CRT 90th	$P = 0.003$, $r = 0.64$ ($N = 19$)				
	FTT (NDOM)	$P = 0.006$, $r = -0.63$ ($N = 17$)				
	PASAT T 2.4	$P = 0.04$, $r = -0.58$ ($N = 13$)				
4a	CRT 90th	$P = 0.0009$, $r = 0.47$ ($N = 30$)		$P = 0.05$, $r = -0.36$ ($N = 30$)		
	FTT (DOM)		$P = 0.027$			
	FTT (NDOM)		$P = 0.008$			
4b	CRT 10th	$P = 0.0004$, $r = 0.70$ ($N = 21$)		$P = 0.014$, $r = -0.53$ ($N = 21$)	$P = 0.0001$, $r = 0.75$ ($N = 21$)	$P = 0.0006$
	CRT 50th	$P = 0.002$, $r = 0.64$ ($N = 21$)		$P = 0.015$, $r = -0.52$ ($N = 21$)	$P = 0.0005$, $r = 0.69$ ($N = 21$)	$P = 0.0008$
	CRT 90th	$P = 0.006$, $r = 0.58$ ($N = 21$)		$P = 0.003$, $r = -0.62$ ($N = 21$)	$P = 0.004$, $r = 0.60$ ($N = 21$)	$P = 0.003$
	FTT (DOM)	$P = 0.0001$, $r = -0.84$ ($N = 21$)		$P = 0.01$, $r = 0.53$ ($N = 21$)	$P = 0.008$, $r = -0.56$ ($N = 21$)	$P = 0.041$
	FTT (NDOM)	$P = 0.0004$, $r = -0.70$ ($N = 21$)		$P = 0.006$, $r = 0.58$ ($N = 21$)	$P = 0.01$, $r = -0.54$ ($N = 21$)	$P = 0.038$
	PASAT T 2.4			$P = 0.007$, $r = 0.82$ ($N = 9$)		

[a] Categorical observations were analyzed using the χ^2-test for contingency tables, whereas continuous observations were assessed by Spearman's rank correlation test (r (s)). KPS, Karnofsky Performance Status; SVAS, sedation VAS.

<table>
<tr><td colspan="11">Tansella CZ, Tansella M, Lader M. A comparison of the clinical and psychological effects of diazepam and amylobarbitone in anxious patients. Br J Clin Pharmacol 1979 Jun; 7(6):605-11.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td colspan="3"></td></tr>
<tr><td></td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="3"></td></tr>
<tr><td>Research Question</td><td colspan="10">To examine the effects of diazepam and amylobarbitone sodium, given in a flexible dosage schedule on simple and complex motor tasks, attention and concentration tasks as well as on objective manifest symptoms and subjective feelings of anxiety.</td></tr>
<tr><td>Drug examined</td><td colspan="10">Barbiturates – Amylobarbitone Sodium (Amytal Sodium) , oral in flexible dosage</td></tr>
<tr><td>Study Design</td><td colspan="10">Double-blind, crossover trial in which the effects of diazepam were compared with those of amylobarbitone sodium and placebo.</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="9">Newly admitted patients with the primary diagnosis of anxiety neurosis. Most complained of insomnia. Informed consent. During the trial no other psychotropic drug was allowed, and no formal psychotherapy was given except of a simple supportive nature.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="9">Patients with obsessional, hysterical or depressive features were excluded.</td></tr>
<tr><td>Study population characteristics</td><td colspan="9">Variable — Values
N = — 24
Age: mean ±SD (range) — 41.7 ±8.7(29-60) years
Number of years of education: mean ±SD — 5.0 ±1
Gender ratio: M/F — 6/18
(Most of the patients were from the lower social class)</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="9">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="10">About a third of the patients were not receiving drugs at the time of initial assessment and the rest underwent a placebo 'wash-out' period of 4-7 days under single-blind conditions. Each drug was given for a week and the drug order was assigned according to a fully balanced Williams' Square design in which each treatment was followed by each other treatment an equal number of times. This allows computation of any possible 'carry-over effects'. Each patients was allocated randomly to one of the six treatment sequences allowed for by the crossover design with the sole constraint that each sequence should be assigned to three females and one male. The conditions were double-blind, neither the doctor adjusting the dosage, the raters nor patients being aware of the identity of the treatment. Each subject was tested on four consecutive weekly occasions. Clinical assessment was always performed the evening before the test session which took place the next morning at 09.00 h, approximately 11 h after the last ingestion. In this session the patients were tested on a comprehensive battery of subjective tests and performance measures. The drugs were administered as identical capsules containing 5mg diazepam, 100 mg amylobarbitone sodium or placebo. The dosage was flexible, ranging from three to nine capsules a day and was determined by the doctor in charge. The capsules were given three times a day and additional capsules were given at night for complaints of insomnia.</td></tr>
<tr><td>Statistical Methods</td><td colspan="10">To correct the carry-over effects due to crossover design used, a full Williams three-way analysis of variance (subjects, drugs, order)(Cochran & Cox, 1957) was carried out on change scores from pretreatment, drug effects being estimated against between-occasion within-subject error variance. The analysis corrected main treatment effects for drug effects which had persisted from the previous week's treatment. Newman-Keul's tests (a t-test for comparing two of a set of means which a F test has shown are not all alike) was computed for the difference between corrected treatment means. Between-patient product moment correlations were calculated between various clinical and demographic data and some measures of drug effect.</td></tr>
<tr><td rowspan="6">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">8.6</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">High Quality</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Y</td><td>N</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="10">1. Personality assessment: Maudsley personality inventory, Manifest anxiety scale, Raven progressive matrices 38
2. Clinical assessment: Hamilton anxiety-rating scale, Morbid anxiety inventory, Anxiety self-rating.
3. Subjective evaluation: Insomnia self-ratings, performance self-rating.
4. Performance measures: Auditory choice reaction time, simple auditory reaction time, card sorting, the digit symbol substitution test (DSST), the symbol coping test (SCT), the Gibson spiral maze (tests motor speed), cancellation tasks, arithmetic, tapping rate.</td></tr>
<tr><td>Results</td><td colspan="10">The mean dosage attained for amylobarbitone sodium was 463 mg/day. Only the variables showing significant drug effects presented.
Self rating of anxiety: Neither placebo nor amylobarbitone sodium affected any significant decrease in subjective anxiety from pretreatment levels. By contrast, diazepam lowered anxiety ratings by almost two-thirds and was very significantly more effective than the barbiturate. No occasions effects were found.
Self-rating of sleep: Both amylobarbitone sodium and diazepam substantially and significantly improved quality of sleep as compared with the placebo week. Occasion effects were not significant.
Performance measures:
• Card sorting: Card sorting into two categories improved over occasions, in accord with the well known effects of practice on this</td></tr>
</table>

	task. • **Cancellation** of consecutive pair's **time** and cancellation of 2's time: A significant occasion effect was found, patients improving over occasions. Amylobarbitone sodium did not affect performance. • **Gibson spiral maze time**: The performance in this test improves significantly over occasions. *After the week's treatment with amylobarbitone sodium,* some improvement over pre-treatment remains, but *performance is significantly impaired as compared to placebo week*. • **Tapping rate**: Patients improved their performance significantly over occasions. Although improvement over pre-treatment remains, *amylobarbitone sodium reduces significantly the tapping rate when compared to placebo.* Correlations with outcome: With amylobarbitone therapy, the only clinical variable to show correlations was rating of poor sleep. This correlated 0.47 (n = 24; P <0.005) with the Maudsley Personality Inventory neuroticism score, -0.57 (P <0.01) with MPI extraversion score and 0.70 (P <0.001) with the Taylor MAS. This suggests that best sleep response to the barbiturate was associated with initially low neuroticism, high extraversion and low trait manifest anxiety. (Table G-51)
Authors' Comments	Both diazepam and amylobarbitone sodium induced a significant self-reported sleep improvement. *Impairment relative to placebo was detected on two motor tests after the barbiturate: tapping rate (simple motor task) and Gibson spiral maze time (more complex psychomotor test) indicating less efficient accuracy and slowing of motor speed*. *Despite the high dosages of both active drugs, patients reported no feeling of hangover* in terms of sleepiness the following morning at the time of rating.

Table G-51. Drug and Occasion Effects

Variable	Means corrected for carry-over effects				t-teststt, 36 df			F-ratio; 2,21 d
	Pre	Placebo	Amylobarbitone	Diazepam	Pl v A	Pl v D	A v D	Occasions
Self-rating of anxiety (mm)	64.2	51.2	59.6	24.2	NS	**	**	0.43
poor sleep (mm)	75.5	70.2	26.5	27.4	**	**	NS	0.46
Card-sorting into two categories (s)	21.5	18.5	19.5	21.5	NS	**	**	4.37*
Gibson maze time (s)	44.5	31.7	35.8	39.3	**	**	**	5.03*
Cancellation task 4's time (s)	65.9	54.0	58.6	73.9	NS	**	**	3.16
2's time (s)	101.6	87.9	90.0	115.5	NS	**	**	4.72
Pair's time (s)	112.0	83.3	91.4	124.4	NS	**	**	5.83**
Tapping rate (number/min)	321.0	341.1	316.1	298.4	**	**	*	10.22**

† computed on change scores from pre-treatment, corrected for carry-over effects.
NS $P > 0.05$. * $P < 0.05$. ** $P < 0.01$.

Vainio A, Ollila J, Matikainen E, Rosenberg P, Kalso E. Driving ability in cancer patients receiving long-term morphine analgesia. Lancet 1995 Sep 9; 346(8976):667-70.

Key Questions Addressed	1	2	3	4	5	6	7	8
		X		X				

Research Question: Do cancer patients receiving long-term morphine analgesia show psychomotor impairment versus patients not on opioids?

Drug examined: Opioids – slow-release oral morphine, dose = 209 mg/day

Study Design: Non-randomized controlled trial design: Cancer patients with pain taking long-term sustained-release oral morphine compared to pain-free cancer patients not taking opioids on psychomotor performance tests.

Population

Inclusion Criteria: Morphine group: Ambulatory cancer patients treated with slow-release morphine tablets (Dolcontin, Pharmacia); dose stable for at least 2 weeks. Patients took morphine tablets twice a day and had a Karnofsky physical performance grade of at least 70 (70 = cares for himself/herself; unable to carry on normal activity or to do active work). Patients were not to be receiving any oncological treatment that could interfere with the tests.

Control group: Controls simultaneously selected from patients treated in the department of radiotherapy and oncology at the same hospital. Ambulatory cancer patients at a similar stage of the disease who had no pain and who did not take any regular analgesics.

Exclusion Criteria: Morphine group: Current treatment with psychotropic drugs, metabolic disturbances, and suspected cerebral metastases or other neurological dysfunctions. (5 patients were on low-dose haloperidol or metotrimeptazine to control nausea; 1patient was receiving small dose of corticosteroids)

Control group: Current treatment with psychotropic drugs, metabolic disturbances, and suspected cerebral metastases or other neurological dysfunctions. (2 patients were on low-dose haloperidol or metotrimeptazine to control nausea; 2 patient were receiving small dose of corticosteroids)

Study Population Characteristics

	Morphine mean (SD)	Control mean (SD)
n	24	25
Age: (yrs)	53(9.4)	51(11.2)
Female / male	12/12	15/10
Primary site of cancer:		
Breast	7	10
Lung	3	3
Gastrointestinal	5	6
Urogenital	7	3
Other	2	3
Duration of disease (weeks)	31 (33)	53 (7.1)
Karnofsky grade (100-0)	80 (8.5)	80 (6.8)
Time om morphine(days)	96 (137)	0 (0)
Morphine dose mg/day	209 (221)	0 (0)
Education		
Basic	11	12
Trade school	5	5
Intermediate	4	5
University	3	3

Generalizability to CMV drivers: Unclear

Procedures: On the study day patients were asked to take the morning dose at 0700. The tests started at 0830 and altogether took about 6h.

Statistical Methods: Student's t-test, Wilcoxon 2-sample test and Kruskal-Wallis Chi-square approximation. Simple linear correlation (Pearson r). $P < 0.05$ was taken as statistically significant.

Quality assessment

Internal Validity	1	2	3	4	5	6	7	8	9	10	11	12	13
	No	No	NR	Yes	No	NR	Yes	Yes	NR	No	NR	Yes	No
4.8 Low Quality	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	
	No	No	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	

Relevant Outcomes Assessed

1. Psychomotor tests: (*Computerized test battery consisting of 5 tests designed for professional drivers and industrial operators)*
   - M30 : matrices tests for nonverbal basic intelligence
   - Q1: Test of capacity for attention (ability to maintain vigilance in monotonous circumstances)
   - LL5: Concentration and structuring ability

	- SET 3: fluency of motor reactions - Peripheral vision test (division of attention, coordination and peripheral vision) 2. Wartegg personality test (Describe the psychological state of the subject in term of such variables as attitude, sense of reality, control and initiative) 3. Neural function tests: - Body sway (Postural control with eyes open and closed) - Finger tapping speeds - Simple reaction time (auditive, visual,associative) - Thermal discrimination on the skin studied by the Middlesex method
Results Q2	Psychomotor tests (Table G-52): *there were no significant differences between groups, though the patients on morphine did tend to perform less well: they were slower and made more errors.* Wartegg personality test (Table G-53): the psychological state of the patients was similar in The 2 groups. Neural function tests (Table G-54): was not grossly worse in those taking morphine: auditory, visual and associative reaction times, thermal discrimination, and postural control with open eyes were about the same. However, *balance with closed eyes was distinctly worse in the morphine group (p <0.05*); *finger-tapping with the preferred hand was better (p <0.05)*. Karnofsky grade and educational background did not influence the results.
Results Q4	The mean plasma concentration of morphine measured in 15 of the morphine group was 66 (SD 79) ng/mL (range: 4.5-337). There was a significant correlation between plasma concentration of morphine and its glucuronide metabolites and poor performance in two of the psychomotor tests- namely Q1 (attention capacity) and LL5 (this test especially demands great power of concentration and good ocular muscle coordination (Table G-55).
Authors' Comments	*Long- term analgesic medication with stable dose of morphine does not have psychomotor effects of a kind that would be clearly hazardous in traffic*. The main relevant observation relevant to driving was a slight dose-dependent effect on the performance of tasks demanding special concentration.

Table G-52. Performance in the "Driving Simulator" Test

Test	Items measured	Morphine group (SD)	Control group (SD)	*P* =
M30 : matrices test for nonverbal basic intelligence	No of correct answers	14.2 (4.6)	14.2 (5.0)	0.956
	No of wrong answer	13.0 (6.0)	11.1 (5.4)	0.245
Q1:test for capacity for attention	Fluctuation (SD) in items processed during 14 periods of 30s	4.2 (1.9)	3.8 (1.6)	0.417
LL5: concentration and structuring ability	Items processed out of 45	18.8 (5.7)	21.3 (6.2)	0.186
	No of errors	1.7 (1.9)	1.5 (1.7)	0.711
SET of 3: Fluency of motor reactions	Time used (s)	432 (299)	369 (102)	0.343
	Number of errors	17.5 (1.9)	10.2 (7.7)	0.285
PVT: Peripheral vision test	Time out of road (s)	5.2 (7.1)	5.2 (4.2)	0.902
Division of attention	Time out of road when disturbed (s)	7.0 (9.8)	6.5 (5.4)	0.817
Coordination and peripheral vision	Peripheral reaction time	2.8 (1.3)	2.4 (1.1)	0.328

Table G-53. Results of the Wartegg Personality Test

Variable	Morphine group mean (SD)*	Control group mean (SD)**	*P* =
Attitude	12.2 (1.8)	12.9 (1.9)	0.266
Sense of reality	18.3 (5.6)	20.5 (7.4)	0.268
Control	2.8 (0.7)	2.7 (0.6)	0.459
Uniformity	3.3 (0.9)	3.3 (0.7)	0.906
Opposition	0.65 (2.0)	1.09 (2.2)	0.512
Initiative	12.0 (2.3)	12.3 (1.9)	0.637

*N = 21; ** N = 23

Table G-54. Neural function tests

Test	Morphine group mean (SD)	Control group mean (SD)	*P* =
Body sway (cm)			
Eyes open	134 (51)	113 (42)	0.178
Eyes closed	263 (136)	184 (82)	0.028
Finger tapping/15s	76 (12)	69 (10)	0.023
Reaction time (ms)			
Auditive	187 (97)	163 (48)	0.289
Visual	291 (64)	277 (72)	0.497
Associative	869 (171)	874 (220)	0.930
Warm test C	1.1 (0.5)	1.0 (0.7)	0.751
Cold test C	0.8 (0.7)	0.5 (0.3)	0.05

Table G-55. Relation between plasma concentration of morphine and its metabolites and the results of the Q1 and LL5 tests

	Plasma morphine	Plasma morphine3-glucuronide	Plasma morphine-6 glucuronide
Q1 test	n =13	n = 13	n =13
	r = 0.74	r = 0.61	r = 0.75
	p <0.005	p <0.05	p <0.005
LL5 errors	n = 10	n = 10	n = 10
	r = 0.85	r = 0.93	r = 0.87
	p <0.005	p <0.001	p <0.001

Study Summary Tables (Key Question 3)

No studies met the inclusion criteria for this key question.

Study Summary Tables (Key Question 4)

Coda BA, Hill HF, Hunt EB, Kerr EB, Jacobson RC, Chapman CR. Cognitive and motor function impairments during continuous opioid infusions. Hum Psychopharmacol 1994; 8:383-400.

Key Questions Addressed	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
		X		X					

Research Question	1. To assess the magnitudes of cognitive and motor effects of morphine and alfentanil at different, steady plasma opioid concentration within the analgesics plasma opioid concentration ranges of the two drugs. 2. To examine the relationships between the magnitude of cognitive and motor effects and plasma concentrations of alfentanil and morphine. 3. To determine whether differences exist in effects of those two mu agonists on cognition or motor function at plasma opioid concentrations considered equally analgesic.	
Drug examined	Opioids – Morphine and alfentanil continuous infusion (Opioids infusion via an IVAC volumetric infusion pump that was controlled by a Macintosh computer).	
Study Design	Double-blind, crossover in 15 healthy volunteers receiving morphine, alfentanil and saline	
Population	**Inclusion Criteria**	15 healthy male volunteers. Subject ranged in age from 21 to 37 years. Literate, proficient in English, in good health and none had a history of drug abuse. Informed consent.
	Exclusion Criteria	
	Study population characteristics	Body weight ranged from 55.4 to 98.6 kg; all were within ±10 per cent of normal weight for height.
	Generalizability to CMV drivers	Unclear
Procedures	Subjects remained seated in a hospital bed inside a sound-attenuated testing chamber throughout each pretest and infusion session. Each subject participated in three pretest sessions on different days; two pharmacokinetic tailoring session involving bolus doses of morphine and alfentanil and one additional session for test battery practice. Each subject participated in three infusion sessions with morphine, alfentanil and saline infused on different days. The order of drug and saline sessions was double-blind and counterbalanced across subjects and a minimum of 7 days separated any two sessions for each subject.	
Statistical Methods	Investigators used a MANOVA for repeated measures (two trial factors) for each of the variables, testing alfentanil, morphine and saline at zero, low, medium and high plasma concentrations. Each analysis yielded an effect for Drug, Target concentration and Drug X Target concentration interaction. Investigators performed *post-hoc* paired t-test where indicated, to determine whether he effects of morphine and alfentanil differed significantly. Investigators performed repeated measures analyses of variance (ANOVA) to contrast changes in spectral edge and delta ratios across the three conditions on scores derived from cortical power spectral analyses of the EEG data. The criterion for statistical significance was alpha = 0.05 in all cases. In addition to analyzing mean differences, we also evaluated the data set for individual differences in treatment effects. Investigators performed a series of multiple regressions with the opioid infusion data (corrected for saline infusion results), in which individual subjects were represented as fixed effects (dummy codes). Each regression predicted performance (motor or cognition) on the basis of different combinations of drug, measured plasma alfentanil or morphine concentration, and individual subject differences.	

Quality assessment														
	Internal Validity	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		NR	NR	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	8.4	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
		Y	Y	Y	NR	Y	Y	Y	Y	Y	Y	NR	Y	NR
	High Quality	**27**	**28**											
		NR	Y											

Relevant Outcomes Assessed	**1**. **Motor performance**: - **Tapping** (*simple* motor performance) - **isometric force**: Maintenance of low constant force with and without visual feedback (indicators of *complex* motor performance) **2**. **Cognitive performance**: - Rapid Single Visual Presentation (**RSVP**). This test measure the speed and accuracy of verbal comprehension. The procedure records the time taken to read words in sentences of a standardized text passage as a measure of comprehension time for individual words. **3. Subjective side- effects**: Subjects rated alertness, nausea, itching and mood using 100 mm visual analog scales (VAS) at baseline and at each target concentration plateau. **4. EEG and sedation:** To evaluate the possibility that the study drugs induced a generalized central nervous system depression.
Results Q4	Target plasma concentration plateaus for alfentanil: 16, 32,64 ng/ml Target plasma concentration plateaus for morphine: 20, 40,80 ng/ml (Table G-56) Motor performance (Table G-57, Table G-59) Error in force maintenance with visual feedback increased from 0.28(SE, 0.02) N at baseline to 0.57 (SE, 0.06) N at the highest alfentanil concentration (64 ng/ml), and from 0.27 (SE, 0.02) N at baseline to 0.63 (SE, 0.11) N at the highest morphine plasma concentration (80 ng/ml). Error in force maintenance without visual feedback was greater at baseline than with visual feedback and this error increased further with increased opioid plasma concentrations. Baseline error of 1.02 (SE, 0.06) N rose to a maximum of 1.75 (SE, 0.15) N at the highest alfentanil plasma concentration, and baseline error of 0.99 (SE, 0.07) N increased to 2.07 (SE, 0.21) N at the highest morphine plateau. While the absolute magnitude of the decrease in accuracy of force maintenance was greater at all time points without visual feedback (i.e., a maximum change of 1.0 versus 0.3N), the changes relative to baseline were about the same with and without feedback. The error in force maintenance approximately doubled at the highest opioid plasma concentration plateau with and without visual feedback. A *post-hoc* comparison of effects of morphine and alfentanil on force maintenance at each drug level revealed no significant differences between the two opioids (paired Student's *t* tests, p = 0.813, 0.24, 0.192, 0.332 at baseline, low, medium, and high opioid concentrations respectively). Thus the highly significant Drug x Target concentration effect is due to differences between the opioids and saline. Cognitive performance (Table G-57, Table G-58, Table G-59): Both opioids exerted minimal effects on *reading time expressed* as *median word time* at the lower target plasma concentrations. However, group averages for median reading time increased by 28 percent at the highest alfentanil target concentration (64ng/ml) and 33% at the highest morphine plateau (80ng/ml). Investigators found a significant Drug x Target concentration effect for the average median reading time. A *post hoc* comparison *(*Student's *t* test) demonstrated significant difference at the low opioid level only (slower median word time with alfentanil (p = 0.029). This difference failed to reach significance when corrected for multiple comparisons (p = 0.116). The effects of alfentanil and morphine on reading speed did not differ significantly from each other at any other target plasma concentration (Student's *t* tests, p = 0.225, 0.029, 0.776, and 0.534 at baseline, low, median and high targets respectively). Saline infusion had no significant effects on reading time; thus, the significant Drug x Concentration effects is mostly due to differences between the opioids and saline. Subjective side effects: The magnitude of each subjective side effect increased with increasing plasma concentrations of morphine and alfentanil.
Authors' Comments	Results show that alfentanil and morphine can impair performance on some but not all motor tasks at analgesic plasma concentrations, and that the magnitude of such impairment is related to plasma opioid concentration. The opioids exerted no significant effects on simple motor tasks or the ability to mobilize force, but they impaired performance on more complex tasks. Investigators found that plasma concentration s of morphine and alfentanil which degraded reading speed and force maintenance had little or no influence on immediate recall of textual information or on rate of repetitive motor activity. Morphine and alfentanil demonstrated no significant effects at any of the plasma concentration studied here on the ability to comprehend the standard narrative passages during drug infusion. At these plasma opioid concentrations, subjects increased time spent reading individual words in order to maintain comprehension and accuracy of recall. Authors conclude that: 1) Continuous infusions of morphine and alfentanil impair some key elements of cognition and motor function within the range of plasma opioid concentration s associated with clinical analgesia. 2) The magnitude of effects on sensitive elements of cognition and motor function are related to plasma concentration with each opioid. 3) The impact of these two mu-agonists on ceratin key aspects of cognition and motor function do not differ at equally analgesic plasma opioid concentrations 4) The therapeutic margins of morphine and alfentanil are nearly identical when cognition and motor effects are considered along with other opioid side-effects such as nausea, sedation, mood alteration and respiratory depression

Table G-56. Bioexponential Equations

	Alfentanil					Morphine				
Subject	Dose wt	*A*	B	*α*	*β*	Dose wt	*A*	*B*	*α*	*β*
1	936	94·1	43·8	0·373	0·0152	7488	405·8	38·5	0·484	0·0115
2	1098	56·7	54·0	0·384	0·0160	8487	1088·1	36·4	0·488	0·0050
3	1250	70·2	38·0	0·265	0·0109	9996	872·8	44·4	0·530	0·0077
4	1005	56·1	34·1	0·384	0·0170	8040	746·2	42·4	0·738	0·0104
5	1194	50·8	29·9	0·132	0·0057	9552	837·4	36·2	0·558	0·0091
6	1170	73·5	48·8	0·287	0·0113	9360	602·9	57·4	0·645	0·0074
7	1245	65·1	37·4	0·255	0·0121	9960	686·5	30·9	0·455	0·0098
8	989	66·1	38·0	0·256	0·0122	9720	802·1	55·4	0·580	0·0106
9	1274	143·3	35·8	0·285	0·0088	10200	540·3	40·4	0·453	0·0106
10	1050	56·1	34·9	0·228	0·0137	8400	420·5	47·5	0·467	0·0098
11	1044	59·3	37·0	0·144	0·0065	8352	696·2	28·9	0·358	0·0074
12	1018	65·4	42·3	0·333	0·0092	8148	585·3	42·2	0·627	0·0101
13	1118	112·8	64·9	0·224	0·0081	8944	686·4	47·6	0·586	0·0102
14	1233	57·3	23·3	0·167	0·0104	9864	741·0	64·3	0·440	0·0081
15	996	80·0	42·2	0·358	0·0100	7968	606·7	50·2	0·706	0·0058
Mean	1107	73·8	40·3	0·272	0·0111	8845	687·9	44·2	0·541	0·0087
SD	—	24·4	9·7	0·081	0·0032	—	169·9	9·5	0·103	0·0018
SE	—	6·5	2·6	0·022	0·0008	—	45·4	2·5	0·027	0·0005
%CV	—	33·1	23·9	29·9	28·8	—	24·7	21·5	19·0	20·9

A and *B* are extrapolated *y*-axis intercepts from biexponential fits. *α* and *β* are hybrid rate constants for drug distributio and elimination.

Table G-57. Multivariate Analysis of Results of Cognitive and Motor Function Measures

Effect measures	df	F	P
Motor performance			
Tapping dominant hand:			
Drug	2,13	2·580	0·114
Target concentration	3,12	2·341	0·156
Drug × target concentration	6,9	1·564	0·262
Tapping nondominant hand:			
Drug	2,13	·396	0·681
Target concentration	3,12	1·316	0·315
Drug × target concentration	6,9	1·761	0·214
2-Finger tapping, alternate hands:			
Drug	2,13	·634	0·546
Target concentration	3,12	·854	0·491
Drug × target concentration	6,9	2·709	0·087
Force maintenance with feedback:			
Drug	2,13	5·084	0·023*
Target concentration	3,12	12·092	0·001*
Drug × target concentration	6,9	2·486	0·106
Force maintenance without feedback:			
Drug	2,13	5·399	0·020*
Target concentration	3,12	35·602	0·000*
Drug × target concentration	6,9	12·069	0·001*
Cognitive performance			
Median word reading time:			
Drug	2,13	6·177	0·013*
Target concentration	3,12	2·848	0·082
Drug × target concentration	6,9	6·043	0·009*

*$p < 0.05$

Table G-58. Mean RSVP Proportion Correct

Target concentration	Saline	Morphine	Alfentanil
Low	0·79 (0·21)	0·82 (0·17)	0·85 (0·22)
Medium	0·80 (0·27)	0·65 (0·22)	0·83 (0·18)
High	0·73 (0·20)	0·77 (0·23)	0·76 (0·19)

Table G-59. Median Word Time and Error Maintenance Without Visual Feedback

Drug	Morphine			Alfentanil		
Target (ng/ml)	20	40	80	16	32	64
Median word time						
Drug plateau	424 (22)	472 (36)	559 (47)	460 (22)	466 (28)	560 (28)
Sham increase	456 (77)	416 (35)	603 (76)	469 (38)	436 (44)	576 (76)
Force maintenance error						
Drug plateau	0·98 (0·08)	1·19 (0·16)	2·07 (0·21)	1·16 (0·14)	1·57 (0·20)	1·75 (0·16)
Sham increase	0·90 (0·12)	1·62 (0·26)	3·05 (0·73)	1·26 (0·23)	1·21 (0·22)	1·41 (0·36)

Values are means (± SE) for 15 subjects at each plateau, and for five subjects at each sham increase. There were no significant differences between plateau values and sham increase values at each level for either drug (Student's *t*-tests).

<table>
<tr><td colspan="15">Kerr B, Hill H, Coda B, Calogero M, Chapman CR, Hunt E, Buffington V, Mackie A. Concentration-related effects of morphine on cognition and motor control in human subjects. Neuropsychopharmacology 1991 Nov; 5(3):157-66.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td></tr>
<tr><td></td><td>X</td><td></td><td>X</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="14">1) To evaluate the sensitivity of each cognitive and motor function measure to morphine, a mu-receptor-selective opioid agonist.
2) To examine the relationships between the magnitude of cognitive and motor effects and concentrations of morphine in plasma.</td></tr>
<tr><td>Drug examined</td><td colspan="14">Opioids – Morphine continuous infusion (Opioids infusion via an IVAC volumetric infusion pump Model 1500 that was controlled by a Macintosh computer).</td></tr>
<tr><td>Study Design</td><td colspan="14">Crossover study in 15 healthy volunteers receiving morphine and saline.</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">15 healthy male volunteers. Subject ranged in age from 21 to 37 years. None reported a history of alcohol or drug abuse and none was currently using medications of any kind. Informed consent.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13"></td></tr>
<tr><td>Study population characteristics</td><td colspan="13">Body weight ranged from 55.4 to 98.6 kg; all were within ±10 per cent of normal weight for height.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="14">Subjects remained seated in a hospital bed inside a sound-attenuated testing chamber throughout each pretest and infusion session. Each subject participated in a pharmacokinetic tailoring session involving bolus doses of morphine and another session for task battery practice. Each subject then participated in infusion sessions with morphine and saline infused on different days. The order of drug treatment was counterbalanced across subjects and a minimum of 7 days separated sessions for each subject.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Morphine and saline results were compared using 2 x 3 (Drug by Infusion Period) repeated-measure analysis of variance (ANOVAs). Planned pairwise comparisons (two-tailed) compared results from the low, medium, and high target plasma concentration periods to their corresponding saline infusion hours.</td></tr>
<tr><td rowspan="6">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">8.2</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td></tr>
<tr><td>N</td><td>NR</td><td>NR</td><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>NR</td></tr>
<tr><td rowspan="2">High Quality</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>NR</td><td>Y</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">1. Motor performance:
- Tapping: Subjects tapped a key using the index fingers of alternate hands, the preferred hand, and the nonpreferred hand as quickly as possible for 7-second trials.
- Isometric force: subject held a small, high-precision isometric force transducer between the index/middle fingers and thumb, maintaining a constant position. Subjects performed 5 tasks. In most cases a visual representation of force magnitude versus time appeared on the computer monitor.
(1) Maximum force
(2) Maintenance of low constant force with visual feedback
(3) Maintenance of low constant force without visual feedback
(4) Fast repetitive changes between two submaximum forces
(5) Targets
2. Visual perception (Lines and letters): The subject indicated whether a sinusoidal display terminated above or below a reference line or completed a letter identification task administered before starting the RSVP passages.
3. Cognitive performance (Verbal comprehension and memory(both immediate and delayed):
- Rapid Single Visual Presentation (RSVP): Words are presented individually on a computer screen.
Following the presentation of a passage and a brief distraction task, comprehension is tested with questions about the content of the passage. We examined the time required to read words.
- End-of-day questions: Final memory test. Questions referred to narrative passaged read during the practice hour and each of the four infusion steps.</td></tr>
</table>

Results Q4	The tree target concentration plateau for morphine was 20, 40 and 80 ng/ml. Tapping (Table G-61, Table G-63, Table G-64) There was a small (0.3 taps per second) decrement in preferred hand tapping at the highest target concentration of morphine. The drug main effect was significant ($p < 0.05$); pairwise comparisons confirmed a significant difference at the high target concentration ($p < 0.001$) The nonpreferred hand tapped faster under morphine than saline for the medium target concentration ($p < 0.00$). We attributed this unexpected finding to the unusually slow saline tapping rate during that period of the saline infusion rather than a true difference from morphine. There were no reliable differences between morphine and saline for the bimanual task, indicating that morphine does not influence the ability to coordinate the hands in the task at the concentration studied. Isometric force (Table G-64): For the targets task, there was a significant Drug by Infusion Period interaction ($p < 0.001$). At the low target concentration, the number of targets hit was higher with morphine than saline ($p < 0.05$) However, at the high target concentration, morphine impaired performance ($p < 0.05$). *The most serious drug effects occurred during the tasks that required the maintenance of low levels of force, with greater deficits when subjects could not rely on vision. In the analysis for maintenance with vision and without vision, absolute error was larger for morphine than saline at the high target concentration ($p < 0.05$ and $p < 0.001$, respectively).*This suggests that vision provides important cues when other sources of information become unreliable. Verbal comprehension and memory(Table G-61,Table G-65): RSVP: *The lowest target concentration of morphine did not impair reading speed, but performance deficits occurred at the medium and high target levels and increase with plasma concentration.*
Authors' Comments	We found strong effects of morphine on some (but not all) cognitive measures and motor function tasks during the steady-state infusions. The degree of impact of this mu-receptor-selective opioid on the drug –sensitive measures was related to plasma concentration of morphine. Morphine also had a strong negative effect on delayed memory. Physicians prescribing morphine on a long-term basis may wish to caution patients that morphine may impair aspects of cognition and motor function. We temper our conclusions about the negative influence of morphine on cognition and motor control with a reminder that we tested healthy volunteers who were not in pain. In patients who are in pain, the presence of pain might cause cognitive and motor effects that would be reduced by the opioids administered to reduce pain. Such effects could occur as a consequence of the distraction caused by pain or as a consequence of the effects of stress on the hypothalamic-pituitary-adrenocortical axis.

Table G-60. Standard Testing Sequence

Time	Task
1–5 min	Three tapping tasks
6–8 min	Visual perception task (lines)
9–30 min	Five force tasks
31–35 min	Apparatus switch
36–37 min	Visual perception task (letters)
38–45 min	RSVP task narrative passage
46–55 min	RSVP task expository passage
56–60 min	Apparatus switch

Table G-61. Summary of Significant Decrements on Cognitive and Motor Tasks

Tapping	
Preferred hand tapping	High*
Nonpreferred hand tapping	None
Bimanual tapping	None
Isometric force	
Maximum force	None
Fast repetitive changes	None
Targets	High
Low force/visual feedback	High
Low force/no visual feedback	High
RSVP	
Reading time	Medium and High
Answers to questions	None

* Refers to target concentration of morphine that produces significant decrements in performance.

Table G-62. Average Measured Plasma Morphine Concentrations

Subject No.	Morphine 20 ng/ml	40 ng/ml	80 ng/ml
1	26.6 (1.6)	55.3 (2.6)	111.7 (8.2)
2	22.5 (2.7)	44.4 (5.3)	92.5 (9.8)
3	22.0 (1.7)	43.1 (3.8)	92.1 (3.7)
4	20.0 (6.3)	51.6 (1.9)	97.7 (6.0)
5	17.4 (3.2)	31.9 (2.5)	65.3 (6.8)
6	12.5 (1.8)	30.4 (1.0)	62.7 (2.7)
7	21.3 (1.0)	38.8 (2.7)	79.1 (0.3)
8	24.7 (3.4)	48.9 (9.0)	73.1 (3.2)
9	19.7 (3.3)	40.5 (3.9)	84.6 (6.1)
10	13.3 (2.8)	31.5 (4.1)	75.9 (1.8)
11	21.7 (1.6)	40.0 (4.5)	60.4 (11.6)
12	21.1 (1.6)	42.0 (2.0)	73.1 (11.4)
13	22.0 (1.4)	42.0 (5.9)	83.1 (7.4)
14	23.5 (4.8)	39.2 (0.6)	86.7 (7.9)
15	16.3 (2.6)	33.1 (2.3)	66.1 (9.2)

* Values are means (SD) of five plasma samples at each plateau.

Table G-63. Mean number of Taps per Second

	Saline	Morphine
	Preferred Hand	
L	5.05 (0.49)	5.01 (0.72)
M	5.12 (0.59)	5.02 (0.61)
H	5.16 (0.62)	4.86 (0.58)
	Nonpreferred Hand	
L	4.42 (0.78)	4.27 (0.73)
M	4.32 (0.76)	4.55 (0.82)
H	4.34 (0.75)	4.45 (0.87)
	Bimanual	
L	7.67 (1.24)	7.46 (1.14)
M	7.68 (1.42)	7.66 (1.15)
H	7.77 (1.32)	7.30 (1.47)

Table G-64. Mean Scores for Forced Tasks

	Saline	Morphine
	Maximum force (Newtons)	
L	108.8 (21.8)	110.3 (21.8)
M	111.3 (22.9)	114.0 (22.6)
H	108.3 (20.3)	106.6 (20.4)
	Fast repetitive changes (number in 20 sec)	
L	104 (35.3)	110 (32.4)
M	104 (32.1)	106 (34.8)
H	105 (34.3)	103 (36.2)
	Targets (Number hit of 10 possible)	
L	7.1 (1.25)	8.0 (1.13)
M	7.5 (1.19)	7.5 (1.36)
H	7.7 (0.98)	6.6 (1.40)
	Maintenance with vision (Absolute error in Newtons)	
L	0.2964 (0.089)	0.3013 (0.713)
M	0.3249 (0.120)	0.3558 (0.125)
H	0.3246 (0.127)	0.6281 (0.420)
	Maintenance without vision (Absolute error in Newtons)	
L	1.0792 (0.544)	0.9843 (0.303)
M	1.2554 (0.492)	1.1887 (0.621)
H	0.9747 (0.252)	2.0721 (0.882)

Table G-65. Mean RSVP Proportion Correct

	Saline	Morphine
L	0.79 (0.21)	0.82 (0.17)
M	0.85 (0.14)	0.65 (0.22)
H	0.71 (0.26)	0.77 (0.23)

<table>
<tr><td colspan="15">Korttila K, Linnoila M. Psychomotor skills related to driving after intramuscular administration of diazepam and meperidine. Anesthesiology 1975 Jun; 42(6):685-91.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td></tr>
<tr><td></td><td>X</td><td></td><td>X</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="14">To examine the effects of Meperidine on psychomotor skills related to driving.</td></tr>
<tr><td>Drug examined</td><td colspan="14">Opioids – Meperidine (intramuscular injection)</td></tr>
<tr><td>Study Design</td><td colspan="14">Randomized, double-blind, crossover in 11 healthy volunteers before, and 1, 3, 5, and 7 hours after intramuscular injection of saline, 10 mg diazepam, or 75 mg meperidine.
The late effects of meperidine were in five other subjects 12 and 24 hours after the injection.</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Eleven healthy student volunteers, eight men and three women. Their medical history indicated good health, and creatinine, alkaline phosphatase, and serum transaminases were normal. None of the subject had had any previous experience with diazepam and meperidine or had taken any medicine for at least a month prior to the experiment. Most used alcohol only occasionally. Informed consent was obtained for the procedure.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13"></td></tr>
<tr><td>Study population characteristics</td><td colspan="13"><u>Variable</u> — <u>Values</u>
n — 11
Age: (yrs.) mean ±SD — 25 ±2.6
Height (cm) mean ±SD — 173.0 ±9.5
Weight (kg) mean ±SD — 67 ±11
Gender M/F — 8 / 3</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="14">Saline placebo, diazepam (Valium), 10mg, or meperidine hydrochloride (Petidin) 75mg, was injected in a volume of 2ml into the muscle of the left thigh at two-week intervals in a double-blind, crossover, randomized (Latin square) fashion. Patients were tested in the morning 1 hour before and 1.3.5.and 7 hours after each treatment. They stayed in a horizontal or slightly recumbent position during the injection and until the one-hour test period.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Additivity of the results and within-cell variances were checked, and thereafter the two-way analysis of variance and student's t test were used for statistical analysis of the data.</td></tr>
<tr><td rowspan="6">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">8.8</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td></tr>
<tr><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>?</td><td>Y</td><td>NR</td></tr>
<tr><td rowspan="2">High Quality</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>NR</td><td>Y</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">1. Subjective assessment: After each test day the subjects were asked whether they thought they had received a tranquilizer, stimulant, or placebo. At every test period they were asked whether they felt tired and how well they felt they could drive. After the whole experiment the subjects were asked which treatment had induced the most pleasant and unpleasant sensation, which had caused the greatest sedative effect and which the greatest pain at the injection site. sedative effect,
2. Psychomotor tests:
a) Reactive skills: Cumulative reaction time and number of mistakes were recorded.
b) Coordinative skills: Two tracking tasks were used to measure hand-eye coordination. The number of mistakes and mistake percentages were recorded. Coordination test I was driven with affixed speed. Coordination test II was driven at a free speed, and the driving time was recorded.
c) Critical flicker-fusion frequency was measured at every test period. Each subject was instructed to announce when a flickering red light (diameter 3 mm) at a distance of 90cm stop flickering.</td></tr>
<tr><td>Results Q2</td><td colspan="14"><u>Subjective assessments and side effects</u>:
Half of the patients injected with diazepam and 73% of those injected with meperidine considered the drug to be a tranquilizer, while more than half of the subjects regarded saline solution as a placebo (Results Table 1). Seven hours after the injection none of the subjects injected with saline placebo was tired, but 9% of those injected with diazepam or meperidine felt tired. There was no recurrence of clinical sedation after that time.
The volunteers' conception of their driving abilities were the most pessimistic 1 to 5 hours after injection of meperidine , but at 7 hours 82% of those injected with either diazepam or meperidine considered their driving ability to be normal. Treatments with meperidine induced the most unpleasant feeling and the greatest sedation and fatigue. The intensities of pain at the injection site were similar after diazepam and meperidine. (Table G-66, Table G-67). After both treatments the thigh became slightly sore and remained that way for the rest of the day, but soreness disappeared by the next morning. Side effects were more common with meperidine. (Table G-68). Two of the volunteers (18%) injected with meperidine experienced syncope after standing up 1 hour after the injection and were unable to perform the test at that time.</td></tr>
</table>

	Despite pre-test training on the apparatus, many subjects continued to improve their performances, especially after the saline solution. This suggests that a training effect continued during the actual trial. Due to the Latin Square this must have influenced all treatments similarly, possibly increasing the standard deviation in each treatment. Test performances **Reactive skills**: Both diazepam and *meperidine significantly impaired the cumulative reaction times, compared with saline solution* (two-way analysis of variance; diazepam P <0.001; meperidine P <0.01), but after the saline injection there was a tendency for improved performances throughout the experiment. The cumulative reaction times remained significantly (P <0.05) worse, compared with saline solution for 3 hours after injection of meperidine and for 5 hours after injection of diazepam. The number of mistakes did not change significantly after any treatment. **Coordinate skills**: Both diazepam and *meperidine significantly (two-way analysis of variance: P <0.01) impaired the parameters measured in coordination test I, compared with saline solution*. The mistakes percentages 5 hours after both diazepam and meperidine were still significantly (P <0.05) higher than after saline placebo, but at 7 hours the results were similar after the two treatments. Driving time did not change significantly. However, subjects treated with saline solution or diazepam had slightly longer driving times after their injections than before, whereas meperidine tended to make the subjects use a faster speed. **Critical Flicker- fusion frequency**: *Only meperidine significantly (two-way analysis of variance: P <0.001) impaired flicker-fusion discrimination, compared with saline placebo*. The ability to discriminate flickering light after meperidine was significantly (P <0.05) worse for 3 hours after the injection and had not yet reached the level of saline placebo at 7 hours. Late effects of meperidine: Since the results of the choice-reaction and flicker-fusion tests 7 hours after meperidine were still worse than after saline solution, we tested another five volunteers of similar ages, weights, heights, and education levels with meperidine. They practised for 2 hours to obtain a constant level of performance and were tested before the injection in the evening. The test battery was then repeated 12 and 24 hours later, the next morning and the following evening. Twelve hours after the injection the parameters measured in coordination test I were significantly (P <0.05) worse and cumulative reaction times slightly worse than those measured at the preinjection tests. The ability to discriminate the fusion of flickering light was no longer affected at 12 hours. All the results at 24 hours were similar to those measured before the injection of meperidine. Drug levels in serum: The highest concentration of diazepam (295 ±82 ng/ml) and meperidine (179 ±66 ng/ml) in serum (means ±SD) were measure 1 hour after injection, after which they declined as function of time with both drugs. Average biological half-lives for diazepam and meperidine were 12 and 4 hours, respectively, as semilogarithmically calculated from the mean values at 3,5, and 7 hours. Those subjects having syncope after meperidine did not have higher concentrations of meperidine in their sera, but nausea and dryness of the mouth seemed to correlate with the meperidine level in the serum. Effects of meperidine: In this study the harmful effets of meperidine on psychomotor performance could be measured for 12 hours, but 24 hours after the injection the performances of all five subjects resembled their preinjection performances. In the present study 2 subjects experienced syncope. This complication should be remembered when patients received the drug as premedication in anesthesia before being fully prepared for surgery.
Results Q4	After meperidine there was a closer correlation between serum levels and psychomotor performance than after diazepam.
Authors' Comments	*Meperidine impaired reactive skills for as long as 3 hours and flicker-fusion discrimination and coordination skills for as long as 12 hours.* It is concluded that patients should not drive or operate machinery for at least 24 hours after receiving 75 mg meperidine intramuscularly. Because of the possibility of syncope after intramuscular administration of meperidine and because of the prolonged impairment of psychomotor skills the drug should not be used in ambulatory practice. One must remember that the results of the present study were obtained in young healthy subjects; the effects of the drug in old or ill patients could be more harmful and more prolonged.

Table G-66. Concepts of Treatments

Treatment	Conception of Volunteers: Placebo (Per Cent)	Tranquilizing Drug (Per Cent)	Stimulating Drug (Per Cent)
Saline solution	64	18	18
Diazepam	36	64	—
Meperidine	9*	73	18

* $P < 0.05$ compared with saline solution ($\chi^2 = 4.91$).

Table G-67. Comparative Subjective Assessment

	Saline Placebo (Per Cent)	Diazepam, 10 mg (Per Cent)	Meperidine, 75 mg (Per Cent)
Most pleasant treatment	46	27	27
Most unpleasant treatment	9	18	73
Greatest sedation and tiredness	—	18	82*
Most painful injection	—	45	55

* $P < 0.05$ compared with saline placebo ($\chi^2 = 6.54$).

Table G-68. Side Effects

	Saline Placebo (Per Cent)	Diazepam, 10 ng (Per Cent)	Meperidine, 75 mg (Per Cent)
Syncope after standing up	—	—	18
Pain at injection site	9	64	55
Nausea	9	—	18
Vertigo	18	—	18
Dry mouth	—	—	36
Headache	—	—	27

Sabatowski R, Schwalen S, Rettig K, Herberg KW, Kasper SM, Radbruch L. Driving ability under long-term treatment with transdermal fentanyl. J Pain Symptom Manage 2003 Jan; 25(1):38-47.

Key Questions Addressed	1	2	3	4	5	6	7	8	9
		X		X					

Research Question

To examine the effects of long- term treatment with transdermal fentanyl on complex psychomotor and cognitive performance measures that are thought to be related to driving ability.

Drug examined

Opioids – Transdermal fentanyl

Study Design

Non-randomized controlled trial design: Individuals with chronic non-cancer pain receiving transdermal fentanyl compared to healthy age and sex matched controls (Fentanyl to control ratio = 1:3)

Study was designed as a non-inferiority trial.

Population

Inclusion Criteria

Fentanyl group: Age =18 to 65 yrs. Outpatients suffering from chronic non-cancer pain responsive to opioids. Treated with transdermal fentanyl for at least 4 weeks without dosage change in the previous 12 days. Valid driving license. Ability to speak and write in German. Informed consent.

Control group: Age =18 to 65 yrs. Controls randomly selected from pool of volunteers. Control sample described as representative of the normal German population with regard to activity, autonomy, and driving experience.

Exclusion Criteria

Fentanyl group: Treated with the following drugs: benzodiazepines of barbiturates >3 times per week; high doses of antidepressant (e.g., ≥75mg amitriptyline per day); antihistamines. Physical disabilities, severe psychiatric or neurological disease, or visual disorder that would prevent performance of study tests.

Control group: Treated with drugs that may affect test performance. Physical disabilities, severe psychiatric or neurological disease, or visual disorder that would prevent performance of study tests.

Study population Characteristics

	Fentanyl group	Control group
n	30	90
Age: (yrs) mean ±SD (range)	50 ±9 (34-65)	50 ±9 (34-65)
Sex: % male	18(60%)	57(63%)
Diagnosis:		
Lower back pain	18	–
Neuropathic pain syndromes	6	–
Miscellaneous	6	–
Duration of pain (months): median (range)	36 (2–216)	–
Pain intensity(NRS) : mean ±SD	3 (0–8)	–
Driving experience (km/yr): median (range)	10,000 (500–60,000)	–
Driving license (years) : median (range)	27 (5–46)	–
Time on fentanyl	At least 4 weeks	0
Plasma fentanyl concentration at the time of testing: median (range)	1.35 ng/ml (0.53-17.7)	0

Generalizability to CMV drivers

Unclear

Procedures

Testing was performed within one week after the screening. Prior to testing, a blood sample was taken to determine the plasma fentanyl concentration, and a urine sample was taken to screen for the use of drugs not reported by the patients. The entire test battery takes about 75 minutes to perform, with the vigilance test at the end taking 25 minutes.

Statistical Methods

Mann-Whitney U-test. A one-sided P-value <0.05 was regarded as significant.

Delta (δ) defined as deficit in test observed when blood alcohol >0.05%.

The sample size needed to demonstrate non-inferiority using 1:1 randomization was calculated as 39 (one-sided t-test, α = 0.05, β = 0.20), assuming no difference between patients, and controls. In order to reduce the required number of patients, we decided to perform a 1:3 randomization, namely, three controls were matched to each patient. This gave a sample size of 26 patients and 78 controls. We therefore aimed to enroll 30 patients to allow for dropouts or protocol violators.

Quality assessment

	1	2	3	4	5	6	7	8	9	10	11	12	13
Internal Validity	No*	No*	Yes	Yes	No*	NR	Yes	Yes	Yes	No*	NR	No*	No*

	14	15	16	17	18	19	20	21	22	23	24	25	
4.2 Low Quality	No*	No*	No*	No*	Yes	Yes	Yes	No*	No*	Yes	No	Yes	

Relevant Outcomes Assessed

1.Attention test (COG)

2.Test for reaction time under pressure, determination test (DT)

3.Test of visual orientation, tachistoscopic perception (TAVT)

	4.Test for motor coordination (2-Hand) 5.Vigilance test (VIG) The primary endpoint was defined as the sum of the scores of the DT, COG, and TAVT tests after z-transformation of the individual scores, using the mean and the standard deviation of the whole sample. Urine screening detected use of unreported drugs such as cocaine, morphine, thebaine, benzodiazepines and antidepressants in 9 cases. Data from these patients were included in the intent-to-treat (ITT) analysis, while the remaining 21 patients without violation of the study protocol were analyzed as the per-protocol (PP) group.
Results Q4	There was a statistical correlation between plasma fentanyl and the items: 'number of error' (P = 0.002), MRT (P = 0.04), and the score (P = 0.01) of the vigilance testing of the PP-group, but fentanyl concentration was not correlated with any of the other items measured.
Authors' Comments	*Results from this study demonstrated that the performance of the patients receiving long-term treatment with transdermal fentanyl was significantly non-inferior to that of the control group*. Patients suffering from chronic non-cancer pain who are treated with a stable dose of transdermal fentanyl do not have a clinically significant impairment of psychomotor or cognitive function which would prevent them from performing complex daily activities, such as driving a car. The results also suggested that the additional intake of illicit drugs can compromise test results. Several variables that might have an impact on performance such as the etiology of the pain and the use of a historical control group for comparison have not been evaluated

Vainio A, Ollila J, Matikainen E, Rosenberg P, Kalso E. Driving ability in cancer patients receiving long-term morphine analgesia. Lancet 1995 Sep 9; 346(8976):667-70.

Key Questions Addressed	1	2	3	4	5	6	7	8
		X		X				

Research Question: Do cancer patients receiving long-term morphine analgesia show psychomotor impairment versus patients not on opioids?

Drug examined: Opioids – Oral morphine: Mean dose = 209 mg/day

Study Design: Non-randomized controlled trial design: Cancer patients on stable maintenance dose of oral morphine compared to cancer patients not on opioids on psychomotor performance tests.

Population

Inclusion Criteria:

Morphine group: Ambulatory cancer patients treated with slow-release morphine tablets (Dolcontin, Pharmacia); dose stable for at least 2 weeks. Patients took morphine tablets twice a day and had a Karnofsky physical performance grade of at least 70 (70 = cares for himself/herself; unable to carry on normal activity or to do active work). Patients were not to be receiving any oncological treatment that could interfere with the tests.

Control group: Controls simultaneously selected from patients treated in the department of radiotherapy and oncology at the same hospital. Ambulatory cancer patients at a similar stage of the disease who had no pain and who did not take any regular analgesics.

Exclusion Criteria:

Morphine group: Current treatment with psychotropic drugs, metabolic disturbances, and suspected cerebral metastases or other neurological dysfunctions. (5 patients were on low-dose haloperidol or metotrimeptazine to control nausea; 1patient was receiving small dose of corticosteroids)

Control group: Current treatment with psychotropic drugs, metabolic disturbances, and suspected cerebral metastases or other neurological dysfunctions. (2 patients were on low-dose haloperidol or metotrimeptazine to control nausea; 2 patient were receiving small dose of corticosteroids)

Study population Characteristics:

	Morphine mean (SD)	Control mean (SD)
n	24	25
Age: (yrs)	53 (9.4)	51 (11.2)
Female / male	12/12	15/10
Primary site of cancer:		
Breast	7	10
Lung	3	3
Gastrointestinal	5	6
Urogenital	7	3
Other	2	3
Duration of disease (weeks)	31 (33)	53 (7.1)
Karnofsky grade (100-0)	80 (8.5)	80 6.8)
Time om morphine(days)	96 (137)	0 (0)
Morphine dose mg/day	209 (221)	0 (0)
Education		
Basic	11	12
Trade school	5	5
Intermediate	4	5
University	3	3

Generalizability to CMV drivers: Unclear

Procedures: On the study day patients were asked to take the morning dose at 0700. The tests started at 0830 and altogether took about 6h.

Statistical Methods: Student's t-test, Wilcoxon 2-sample test and Kruskal-Wallis Chi-square approximation.
Simple linear correlation (Pearson r). P <0.05 was taken as statistically significant.

Quality assessment

Internal Validity	1	2	3	4	5	6	7	8	9	10	11	12	13
	No*	No*	No*	Yes	No*	NR	Yes	Yes	NR	No*	NR	Yes	No*
4.7 Low Quality	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	
	No*	No*	Yes	No*	Yes	Yes	Yes	No*	No*	Yes	Yes	Yes	

Relevant Outcomes Assessed:

1. Psychomotor tests: (Computerized test battery consisting of 5 tests designed for professional drivers and industrial operators)
   - M30 : matrices tests for nonverbal basic intelligence
   - Q1: Test of capacity for attention (ability to maintain vigilance in monotonous circumstances)

	- LL5: Concentration and structuring ability - SET 3: fluency of motor reactions - Peripheral vision test (division of attention, coordination and peripheral vision) 2. Wartegg personality test (Describe the psychological state of the subject in term of such variables as attitude, sense of reality, control and initiative) 3. Neural function tests: - Body sway (Postural control with eyes open and closed) - Finger tapping speeds - Simple reaction time (auditive, visual,associative) - Thermal discrimination on the skin studied by the Middlesex method
Results Q4	The mean plasma concentration of morphine measured in 15 of the morphine group was 66 (SD 79) ng/mL (range: 4.5-337). There was a significant correlation between plasma concentration of morphine and its glucuronide metabolites and poor performance in two of the psychomotor tests- namely Q1 (attention capacity) and LL5 (this test especially demands great power of concentration and good ocular muscle coordination) (Table G-69).
Authors' Comments	Long- term analgesic medication with stable dose of morphine does not have psychomotor effects of a kind that would be clearly hazardous in traffic. The main relevant observation relevant to driving was a slight dose-dependent effect on the performance of tasks demanding special concentration.

Table G-69. Relation between plasma concentration of morphine and its metabolites and the results of the Q1 and LL5 tests

	Plasma morphine	Plasma morphine3-glucuronide	Plasma morphine-6 glucuronide
Q1 test	n = 13 r = 0.74 p <0.005	n = 13 r = 0.61 p <0.05	n = 13 r = 0.75 p <0.005
LL5 errors	n = 10 r = 0.85 p <0.005	n = 10 r = 0.93 p <0.001	n = 10 r = 0.87 p <0.001

Study Summary Tables (Key Question 5)

No studies met the inclusion criteria for this key question.

Study Summary Tables (Key Question 6)

<table>
<tr><td colspan="12">Sellers EM, Schneiderman JF, Romach MK, Kaplan HL, Somer GR. Comparative drug effects and abuse liability of lorazepam, buspirone, and secobarbital in nondependent subjects. J Clin Psychopharmacol 1992 Apr;12(2):79-85.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>x</td><td></td><td></td></tr>
<tr><td>Research Question</td><td colspan="11">What is the abuse liability of lorazepam, buspirone and secobarbital in non-dependent, non-abusing subjects?</td></tr>
<tr><td>Drug examined</td><td colspan="11">Schedule II - secobarbital (compared to buspirone and lorazepam)</td></tr>
<tr><td>Study Design</td><td colspan="11">Double-blind randomized crossover</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="10">Male subjects, experienced non-therapeutic users of at least two CNS depressants, at least one in pill or capsule form, with ingestion averaging no greater than 3 times per week in the last 6 months. Non-dependent, non-abusing population with significant drug use experience to be familiar with drug effects.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="10">A positive urine drug test for alcohol, amphetamines, cocaine, benzodiazepines, narcotics, cannabinoids, and barbituates. Excluded if did not pass physical exam.</td></tr>
<tr><td>Study population characteristics</td><td colspan="10">26 subjects, male, mean age of 31, range of 21-47.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="10">Not known</td></tr>
<tr><td>Procedures</td><td colspan="11">One hour after a light breakfast, subjects received buspirone 10 mg, buspirone 20 mg, lorazepam 2 mg, secobarbital 100 mg or placebo. Subjects tested on 5 study days at least one week apart. 1,2, and 4 hours after ingestion of drug, Profile of Mood States questionnaire administered, perceived drug effect, drug strength and drug liking measured on a 1-7 point scale. Motor performance evaluated with visual tracking task. Subject used joystick to maintain an airplane over a moving road shown on an oscilloscope. Memory task of word recall.</td></tr>
<tr><td>Statistical Methods</td><td colspan="11">Data considered separately for five-time points: the actual values at 1,2, and 4 hours post-drug; the peak of the post-drug values; the mean of the three post-drug values. For each such point, baseline scores were used as a covariate and adjusted scores entered into direct-difference t tests. Newman-Keuls Studentized range procedure used to reinterpret the significance of these t tests due to multiple components involved.
Statistics seemed appropriate.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td></tr>
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<tr><td rowspan="2">7.7
Low</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="11">Motor performance (visual tracking test) and cognitive (memory) test.</td></tr>
<tr><td>Results</td><td colspan="11">The Schedule II drug (secobarbital) had little or no effect on performance on the tests while lorazepam had significant effects. (Table G-70)</td></tr>
<tr><td>Authors' Comments</td><td colspan="11">Secobarbital was used at its usual clinical dose of 100 mg. Authors thought they might be able to see a significant effect at a higher dose.</td></tr>
<tr><td>Reviewers' Comments</td><td colspan="11">Well-designed study showed little or no effect of secobarbital on indirect tests of driving performance 1,2, and 4 hours of ingestion. Would be interesting to see what a higher dose would do as the authors suggested. Would also be interesting to see effect of dose taken at night, the usual treatment for sleep disorders.</td></tr>
</table>

Table G-70. Results

	Hour		
	1	2	4
Rating scale: drug effect	PLSbB	PbSBL	PSbBL
Rating scale: drug liking	BPbSL	BPbLS	NS[a]
Rating scale: drug strength	PBSbL	PbSBL	PSbBL
Tracking task, maximum distance	bPBSL	bPBSL	bBPSL
Tracking task, % of time over road	LSBPb	LSBbP	LSBPb
Tracking task, average distance	bPBSL	PBBSL	bBPSL
Postural stability, eyes open	NS	bSPBL	SPbBL
Postural stability, eyes closed	NS	SPbBL	NS
Uncued recall, one presentation	LSBbP	LSPBb	NS
Uncued recall, two presentations	LBbSP	LSbBP	LBSbP
Uncued recall, overall	LBSbP	LSPBb	LSbBP
Total recall, one presentation	LBSbP	NS	NS
Total recall, two presentations	LBSbP	LSBbP	NS
Total recall, overall	LBSbP	LBPbS	NS
ARCI[b] scale: benzedrine	NS	NS	LBbPS
ARCI scale: pentobarbital	NS	PbSBL	PSbBL
POMS[c] scale: arousal	NS	LBSbP	NS
POMS scale: confusion	NS	PbBSL	SPBbL
POMS scale: depression-dejection	NS	NS	BPbSL
POMS scale: fatigue	NS	NS	SbPBL
POMS scale: positive mood	NS	NS	LPSBb
POMS scale: tension-anxiety	NS	NS	SPbBL

P = placebo; b = buspirone 10 mg; B = buspirone 20 mg; L = lorazepam 2 mg; S = secobarbital 100 mg. Letters sharing an underline indicate drug doses that did not differ significantly by a post-hoc Neuman-Keuls test, $\alpha = 0.05$.

[a] NS = not significant.

[b] ARCI = Addiction Research Center Inventory.

[c] POMS = Profile of Mood States.

Westerling D, Frigren L, Hoglund P. Morphine pharmacokinetics and effects on salivation and continuous reaction times in healthy volunteers. Ther Drug Monit 1993 Oct;15(5):364-74.

Key Questions Addressed	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
						X		

Research Question: To investigate the plasma concentration profile and absolute bioavailability of morphine controlled release (CR), and explore the possible relationship between plasma concentration and drug effects

Drug examined: Opioid: Morphine (I.V., oral solution or controlled release (CR) tablet.

Study Design: Randomized, 0pen label, crossover design in which 10 healthy male volunteers were given an I.V. infusion of 10 mg morphine HCL, and oral solution of 20 mg morphine HCL, or a new controlled release (CR) tablet of 30 mg morphine sulfate on three separate occasions.

Population

Inclusion Criteria: All subjects were found to be healthy in clinical examination and all had blood and urine chemistry values within normal ranges. Informed consent.

Exclusion Criteria: NR

Study population characteristics

Variable	Values
n	10
Age (yrs.):	25-56
Gender M/F	6 / 4
Weight (kg) mean	73.1 ±12.6

Generalizability to CMV drivers:

Procedures: All subjects received three treatments -A, B, and C- in a randomized order. There was at least *1 week washout between treatments.*

Treatment A: Subjects received an *I.V. infusion of 10 mg morphine HCL* for 20 min. Salivation was measured before infusion and at 3,20,50,80, and 110 min and every hour for 14 h after the start of the infusion. Continuous reaction times (CRTs) were recorded before the infusion and at 10 and 30 min and every hour for 6h after the start of the infusion.

Treatments B: Subjects received *20 mg morphine HCL orally*. Salivation was measured before infusion and at 10,30,50,70, 110, and 140 min and every hour for 14 h following ingestion of the morphine solution. CRTs were recorded before, 20 min after, and every hour for 6h after the oral solution was given.

Treatment C: Subjects received *30 mg morphine sulfate orally (CR tablets)*. Salivation was measured before infusion and at 20, 50, 80, and 110 min and every hour for 14 h after the CR tablet was given. CRTs were recorded before, 30 min after, and every hour for 12h after the CR tablet was given.

Statistical Methods: Since this was the first study of the new CR preparation, the number of subjects could not be based on power calculation. Results are generally presented as mean ±SD, median, or 95% Cis. For comparison of ratios between treatments, log-transformations were performed and geometric means and CIs given In the present study, comparisons of interest are , in most cases, between two treatments; a two-tailed *t*-test for paired samples was then used. The significance level was set to 5%.

Quality assessment

Internal Validity	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
	Y	NR	NR	Y	NR	NR	Y	Y	Y	Y	Y	Y	N
6.3	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
	N	N	N	N	Y	Y	Y	Y	Y	Y	N	Y	NR
Moderate Quality	**27**	**28**											
	NR	Y											

Relevant Outcomes Assessed: **Continuous Reaction Times** (**CRT**): Subjects were exposed to a series of auditory signals from earphones, to which they were instructed to react as quickly as possible by pressing a button. Signals were delivered by a computer and reaction times were recorded. Signals were presented at random intervals of 2-5 sec, 15 signals per min.

Results Q6: All volunteers tolerated the three form of administration of morphine well. After I.V. infusion of morphine , subjects felt slightly drowsy.

Reaction Times are known to have skewed distributions, and, therefore, values are given as 10, 50, and 90 percentile, where the 10th percentile represents fast reaction time, and the 50th represents median reaction time, ant the 90th percentile represents slow reaction time.

A significant slight prolongation of mean CRT was found as was a markedly increased variability in reaction times at the higher plasma morphine concentration obtained after I.V. infusion.

Authors' Comments: Non analgesic effect of morphine, studied as increased variation of CRTs, were related to plasma concentrations of morphine and found to be most pronounced at the higher plasma concentrations obtained after I.V infusion.

As could be expected from CR formulation, a prolonged Tmax and lower maximal plasma concentration was found after administration of CR tablet than after administration of oral solution of morphine. There was no difference in bioavailability between the two oral preparations, but an interindividual variation in plasma concentration of morphine was found regardless of the method of administration.(Table G-71)

Plasma concentration produced after intake of the CR tablet were lower than after intake of immediate release morphine solution, but were maintained at a plateau level for at least 12 h. At 6, 12, and 24 h after the CR tablet was given, mean plasma concentrations were

	11.3 ±6, 5.6 ±3.3, and 6.1 ±1.3 nmol/L, respectively. The t 1/2 for morphine after I.V. infusion was 1.56 ±0.61h

Table G-71. Cmax, Tmax, and the Absolute Bioavailability of Morphine

	C_{max}		T_{max}		F	
Subject	Sol (nmol/L)	CR (nmol/L)	Sol (h)	CR (h)	Sol (%)	CR (%)
1	54.7	10.8	0.8	10	21.6	20.6
2	51.9	77.2	1	3	22.8	18.7
3	77.8	22.3	1	5	32.8	18.8
4	36.7	7.7	0.8	5	8.3	11.1
5	29.5	5.8	0.3	24.2	8	7.6
6	31.5	9.5	0.5	5	19.4	8.5
7*	63.6	11.8	0.5	3	27.7	16.3
8	105.6	20.2	0.3	2	32.1	26.5
9	46.8	19.3	0.3	4	17.8	18.4
10	49.3	27.8	1	5	25.2	24.4
Median			0.65	5		
Mean	54.7	15.6			21.6	17.1
SD	23.1	7.4			8.6	6.3
CI	38.2–71.3	10.3–20.8	0.4–0.9	3.5–13.6	15.4–27.7	12.6–21.6

CR, controlled release tablet; sol, oral solution.

Zawertailo LA, Busto U, Kaplan HL, Sellers EM. Comparative abuse liability of sertraline, alprazolam, and dextroamphetamine in humans. J Clin Psychopharmacol 1995 Apr;15(2):117-24.								
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
						x		
Research Question	What is the comparative abuse liability of sertraline, alprazolam and dextroamphetamine in humans?							
Drug examined	Schedule II drug (dextroamphetamine) compared to setraline, alprazolam							
Study Design	Blinded randomized crossover study.							
Population	**Inclusion Criteria**	Male volunteers who had taken sedative or tranquilizer drugs. Experienced users of two or more CNS depressants in the past year, at least one in tablet or capsule form, including cannabis and alcohol. Normal medical history and physical including EKG and laboratory screen, weight within 30% of ideal weight.						
	Exclusion Criteria	No diagnosis of DSM-III-R psychoactive substance abuse disorder in the past year. No drug or substance abuse within 72 hours of the test. Confirmed by urine analysis.						
	Study population characteristics	20 male volunteers, mean age 27 (range, 19 to 47)						
	Generalizability to CMV drivers	Unknown. Do CMV drivers use amphetamines to stay awake during long drives?						
Procedures	Subjects were given placebo, alprazolam, 1 mg; dextroamphetamine, 10 mg; sertraline, 100 mg; or sertraline, 200 mg. Two baseline tests administered, then tests at 1, 2, 3, 4, 5 and 8 hours postdrug. Objective test was a manual tracking test in which the subject uses a joystick to control an airplane shape over a moving image of a road. Subjective tests were Addiction Research Center Inventory, Profile of Mood States, Drug Perception and Performance Profile and Checklist for Adverse Reactions. An observer related instrument, the Drug Elicited Behavior Inventory was also included.							
Statistical Methods	Used SAS, General Linear Models for analysis of variance, t-tests, and planned contrasts.							

Quality assessment	**Internal Validity**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
		14	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
		N	Y	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	NR
		27	**28**											
		NR	Y											

Relevant Outcomes Assessed	Motor activity assessed by manual tracking test.
Results	D-amphetamine did not have a significant effect on results of the manual tracking test at any timepoint (1-8 hours postdrug) compared to placebo. In contrast, alprazolam did negatively impact performance on the manual tracking test decreasing percent of time over the road. (Table G-72, Table G-73, Table G-74)
Authors' Comments	With regard to d-amphetamine - This drug showed only positive effects of euphoria, liking, and elation with no sedation or confusion. While not impairing motor activity this drug has the highest potential for abuse.

Table G-72. Peak Objective and Subjective Effects of Sertraline 100mg, 200mg, Alprazolam 1.0mg and b-amphetamine 10mg on selected scales that show significant difference among drug conditions

Drug Condition	Sertraline 100 mg	Sertraline 200 mg	Alprazolam 1.0 mg	D-amphetamine 10 mg
Manual tracking task	0	0	–	0
POMS				
Elation	0	0	+	+
Confusion	0	0	+	0
Arousal	0	0	–	+
ARCI				
MGB	0	0	+	+
LSD	0	+	0	+
PCAG	0	0	+	–
A	0	0	+	+
Cole/ARCI				
Abuse-potential	0	0	+	+
Physical-unpleasantness	0	+	0	0
DPPP				
Liking	0	0	0	+
Pleasant on mind	0	0	+	+
Pleasant on body	0	0	+	+
Drug strength	0	+	+	0

[a] POMS, Profile of Mood States, ARCI, Addiction Research Center Inventory.
(+) indicates a significant increase in peak response compared with placebo, (–) indicates a significant decrease in peak response compared with placebo, and (0) indicates no significant change in peak response compared with placebo ($p < 0.05$).

Table G-73. Area Under the Curve Measures for Objective and Subjective Effects of Sertraline 100mg, 200mg, Alprazolam 1.0mg and b-amphetamine 10mg on selected scales that show significant difference among drug conditions

Drug Condition	Sertraline, 100 mg	Sertraline, 200 mg	Alprazolam, 1.0 mg	D-amphetamine, 10 mg
Manual tracking task	0	0	–	0
POMS				
Elation	0	0	+	0
Confusion	0	0	+	0
Arousal	0	0	–	+
ARCI				
MGB	0	0	+	+
LSD	0	+	0	+
PCAG	0	0	+	–
A	0	0	0	+
Cole/ARCI				
Abuse-potential	0	0	0	0
Physical-unpleasantness	0	+	0	0
DPPP				
Liking	0	0	0	0
Pleasant on mind	0	0	+	0
Pleasant on body	0	0	+	0
Drug strength	0	0	+	+

[a] POMS, Profile of Mood States, ARCI, Addiction Research Center Inventory.
(+) indicates a significant increase in peak response compared with placebo, (–) indicates a significant decrease in peak response compared with placebo, and (0) indicates no significant change in peak response compared with placebo ($p < 0.05$).

Table G-74. Manual tracking performance with d-amphetamine [a]

Manual tracking task (peak response)	NS
Manual tracking task (area under the curve)	NS

NS = Not Significant

[a] To simplify analyses the subject and baseline effects were removed from the data by use of the General Linear Models (GLM) procedure, leaving an adjusted data set (statistically equivalent to taking subject and baseline effects as covariates. For each dependent variable, statistics analyzed were adjusted scores at 1,2,3,4,5 and 8 hours postdrug, the peak score (when the appropriate direction could be defined), and the area under the curve (AUC) from hours 0 to 8, computed as the simple area

under the polygon with the baseline score as the 0 level. From this analysis, t-tests comparing a pair of drug conditions (using a common error term) were performed, with no adjustment for the number or nonorthoganlity of these tests. A p value of less than 0.05 for the t-tests was considered statistically significant.

Study Summary Tables (Key Question 7)

No studies met the inclusion criteria for this key question.

Study Summary Tables (Key Question 8)

<table>
<tr><td colspan="15">Clark CR, Geffen GM, Geffen LB. Role of monoamine pathways in the control of attention: effects of droperidol and methylphenidate in normal adult humans. Psychopharmacology 1986; 90(1):28-34.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td></tr>
<tr><td></td><td>X</td><td></td><td></td><td></td><td></td><td></td><td>X</td><td></td></tr>
<tr><td>Research Question</td><td colspan="14">To examine the effect on auditory selective attention of methylphenidate and droperidol administered intravenously to normal volunteers.</td></tr>
<tr><td>Drug examined</td><td colspan="14">Methylphenidate hydrochloride (Ritalin ®) - (0.65 mg/kg) IV</td></tr>
<tr><td>Study Design</td><td colspan="14">Randomized, crossover in 12 male volunteers receiving methylphenidate, droperidol or placebo.</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Twelve right handed male volunteers between the ages of 18 and 30 years who were screened for medical and psychiatric abnormalities. Normal hearing range was assessed by pure tone audiometry, with the maximum acceptable hearing loss on each ear being 25 decibels (ISD) between 125 and 4000Hz.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13"></td></tr>
<tr><td>Study population characteristics</td><td colspan="13">Twelve right handed male volunteers between the ages of 18 and 30 years</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13">Unclear</td></tr>
<tr><td>Procedures</td><td colspan="14">Each subject was informed of the drugs to be used and their possible side effects.
At the beginning of each session either 15 µg / kg droperidol or placebo was administered and this was followed 1 h later by the administration of either 0.65mg/kg methylphenidate or placebo. The delay of 1 h in each session between drug administrations was introduced to allow the antagonist action of droperidol to take full effect.
Methylphenidate hydrochloride (Ritalin®) was provided in 20 mg dry ampoules. Droperidol (Dropleptan®) was provided as 10 mg in 2ml ampoules. Drugs and placebo were administered in 10 ml solution over 5 min via an indwelling intravenous cannula on the dorsum of the hand.
Four drug sequences were employed: 1) placebo followed by placebo (placebo condition), 2) placebo followed by methylphenidate (methylphenidate condition), 3) droperidol followed by placebo (droperidol condition), 4) droperidol followed by methylphenidate (droperidol + methylphenidate condition)
Testing started approximately 20 min after the second injection and lasted approximately 1h.
Subjects we seated in a sound attenuated-room and received their instructions through a two-way intercom. set. The subjects listened to pairs of words and depressed one of two microswitches using the forefinger ipsilateral to the ear in which predesignated target words were detected. Before each list subjects we shown a card containing the relevant target word and distractor word.
Attention conditions (divided or focused) were ordered randomly provided that the divided attention strategy was completed either first or last in order to limit any strategy priming effects.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Divided and focus attention scores from each drug conditions (methylphenidate, droperidol, droperidol + methylphenidate) were compared with those from the placebo conditions using repeated measures analysis of variance. Post hoc analyses were conducted where necessary using the Fisher test in order to interpret significant interactions. Cardiovascular parameters and questionnaire scores from each of the three drug conditions were also compared to placebo using repeated measures analysis of variance.</td></tr>
<tr><td rowspan="6">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td></tr>
<tr><td rowspan="2">8.8</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td></tr>
<tr><td>N</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>Y</td><td>N</td><td>Y</td><td>NR</td></tr>
<tr><td rowspan="2">High Quality</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>NR</td><td>Y</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">1. Dichotic monitoring: Subjects were administered a dichotic monitoring task in which they were required to detect nominated target words and discriminate them from phonemic distractors. In each of the four test sessions in which drugs were administered, subjects performed one list in which they were required to divide their attention equally between the left and right ear stimuli (divided attention) and two lists in which they were required to focus their attention on either the left or right ear and to ignore the other (focused attention).
The dependent measures obtained from the dichotic monitoring tasks were:
A. .Ipsilateral target detection rate
B. Ipsilateral plus contralateral rate of response to distractors (error rate)
C. Ipsilateral response time to targets and a signal detection measure of target discrimination
(target detection rate-error rate)
2. Cardiovascular effects
3. Subjective state: Immediately, before testing during each drug session, subjects were asked to complete a questionnaire designed to assess their subjective state on the six dimensions of anxiety, alertness, elation, lethargy, relaxation and depression. (These constructs were drawn from the Brief Psychiatric Rating Scale and the Inpatients Behavioral Rating Scale). The subjective state</td></tr>
</table>

	questionnaires were scored by coding from 1 to 7, with 1 representing the pole "not at all" and 7 representing "extremely so".
Results	Methylphenidate administered 1h after droperidol treatment reversed all signs of withdrawal and depression. On addition, subjects made comments such as "feel relax and alert", "feel good now". "feel terrific now" and "ready for action". Four subjects made comments which indicated than following droperidol certain of the subjective effects of methylphenidate were less intense than when methylphenidate was administered alone. For example three subjects mentioned than although they experienced euphoria and talkativeness as before, it lasted for a considerably shorter period. Only 2 subjects commented on the ability to concentrate: both mentioned being easily distracted, and one mentioned losing his train of thought more often than normal though he could "bring himself back" once this was realized. Only one subject commented on perceptual experiences when methylphenidate had reversed the effects of droperidol: " this (methylphenidate is very much an outlook sensation drug which means you respond to a lot of different things at the same time …I am aware of my scope of vision … trying to take everything in at once". (Table G-75)
Authors' Comments	Performance following placebo was superior when attention was on one ear than when divided between the ears. Administered alone, methylphenidate had no effects on dichotic measures of attention but had marked effects on spontaneous behavior, when most subjects reported a substantial increase in both the field and distractibility of attention. The disparity between the subjective and objective assessments of the effects of the drug on attention is discussed in terms of the degree of mental effort voluntarily brought to bear by subjects in the selective allocations of their attentional capacity.

Table G-75. Mean error rates (%) during divided and focused attention in the different drug conditions. Left and right channel performance has been summed and averaged in each divided attention condition. Focused attention means are the average of the attended left and attended right channels. Figures in parentheses represent standard errors

	Divided attention	Focused attention
Placebo	16.4 (2.3)	20.8 (3.1)
Methylphenidate	14.1 (3.5)	15.4 (2.4)
Droperidol	12.8 (2.0)	19.0 (3.0)
Droperidol + methylphenidate	11.2 (1.6)	16.9 (3.4)

<table>
<tr><td colspan="15">Forrest WH Jr, Brown BW Jr, Brown CR, Defalque R, Gold M, Gordon HE, James KE, Katz J, Mahler DL, Schroff P, Teutsch G. Dextroamphetamine with morphine for the treatment of postoperative pain. N Engl J Med 1977 Mar 31; 296(13):712-5.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>x</td><td></td></tr>
<tr><td>Research Question</td><td colspan="14">To examine the clinical utility of dextroamphetamine and morphine together for the treatment of postoperative pain</td></tr>
<tr><td>Drug examined</td><td colspan="14">Opioid and stimulant: Morphine sulfate (3, 6,or 12mg) and dextroamphetamine (5 or 10 mg), intramuscularly</td></tr>
<tr><td>Study Design</td><td colspan="14">Randomized, double-blind, single-dose</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Subjects were patients on the surgical wards of five member hospitals of the Veteran Administration Cooperative Analgesic Study who had been identified before operation as likely to have severe postoperative pain, as able to tolerate morphine 12mg, with dextroamphetamine, 10 mg, and a free of major organ- system disease.</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">NR</td></tr>
<tr><td>Study population characteristics</td><td colspan="13">Variable — Values
n — 450
Age (yrs.): mean — 35
Gender M/F — 444 / 6
Surgical procedures were primarily abdominal or orthopedic.</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13"></td></tr>
<tr><td>Procedures</td><td colspan="14">There were between 6 and 12 patients in each treatment group per hospital, from 46 to 52 in each group overall. A treatment consisted of morphine sulfate, 3, 6 or 12 mg, combined with dextroamphetamine, 0, 5, or 10 mg, assigned randomly (One combination to each patient) and administered intramuscularly double-blind (See table 1).</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">We made no attempt to control for preanesthetic medication or anesthetic procedure.
Analgesic and performance data were analyzed with parallel-line bioassay technics to estimate the potency of dextroamphetamine combined with morphine relative to morphine alone. Simple t-tests were done to establish significance of treatment-group differences for side-effect data.</td></tr>
<tr><td rowspan="4">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
<tr><td>Yes</td><td>NR</td><td>NR</td><td>Yes</td><td>NR</td><td>NR</td><td>Yes</td><td>NR</td><td>NR</td><td>Yes</td><td>NR</td><td>No*</td><td>Yes</td></tr>
<tr><td rowspan="2">6.2
Moderate Quality</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td></td></tr>
<tr><td>NR</td><td>Yes</td><td>Yes</td><td>NR</td><td>No*</td><td>Yes</td><td>Yes</td><td>Yes</td><td>Yes</td><td>NR</td><td>Yes</td><td>Yes</td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">1. Relief of pain was determined with standard technic involving trained nurse observers who elicited patients' subjective responses. Six interviews were conducted at 45- minute intervals after medication. Pain relief was scored as complete (4), good (3), moderate (2), slight (1), or no relief (0). Scores were summed for all observations to provide an estimate of analgesia.
2. Performance tests: three performances tests were used to measure the patient's general alertness- tapping speed, simple arithmetic and symbol copying.
- Tapping speed has been shown to be sensitive to the delayed effects of night-time hypnotics. We used it was it as an objective measure of sedation. The patient tapped his thumb on a hand tally counter as rapidly as possible, and the total number of taps per trial was recorded. The test involved three 10-second tapping trials and one 30 seconds, with a 15-second interval between trials.
- The arithmetic tests consisted of 16 problems: four each in addition, substraction, multiplication and division.
- Symbol copying test were derived from the wechsler Intelligence Scale for Adults and is considered a measure of cognition or perception and has been shown to be sensitive to depressants. The test seemed to us a good indicator of patients' ability to understand nurses' instructions.
All tests were done before operation to determine base-line performance and again at the three posmedication interviews.
3. Blood pressure, pulse and respiratory rate were recorded before treatment and at all postmedication interviews. Patients were questioned about whether they had dizziness, headache, nausea, sleepiness, sweating, or vomiting. Other side effects volunteered by the patients or observed by the nurse were recorded.</td></tr>
<tr><td>Results</td><td colspan="14">Total relief pain increased with increased doses of morphine (except for morphine, 6 mg, combined with dextroamphetamine, 5 mg). Both dextroamphetamine groups produced greater relief of pain than did morphine alone and there was an increase effect with increased doses of dextroamphetamine. When we compared data for the combination of dextroamphetamine, 10 mg, with morphine with those for morphine alone, using standard bioassay statistical methods, we found that the combination was twice as potent as morphine alone. For example, the relief of pain for morphine, 6mg, given with dextroamphetamine, 10 mg, was about the same as that reported for 12 mg of morphine alone. The combination of dextroamphetamine, 5 mg, with morphine enhanced the analgesic potency of morphine by a factor of 1.5. The time course of action for analgesic effect up to 4.5 hours was similar for morphine alone and for both combinations when equipotent treatments were compared.
Performance tests: In proportion to its dose, dextroamphetamine generally improved performance that was decreased by morphine. The best example of effect was found in the results for the 30-second tapping speed. As the morphine dose was increased, performance decreased, suggesting greater sedation. On the other hand, performance improved with increasing doses of dextroamphetamine. Significant dose-response relation were found (P <0.05) for morphine and both combinations. Results of the arithmetic and symbol-copying tests followed the same pattern, although there was some suggestion of a biphasic effect for</td></tr>
</table>

	dextroamphetamine on the arithmetic test. Effects on blood pressure, pulse and respiratory rate were minimal. All post-treatment means were up to 10 per cent higher than base line for systolic and diastolic pressure; changes in pulse rate ranged from 10 to 20 per cent higher than base line; the mean respiratory rate for all patients was two breaths per minute faster during study than it was before medication. **Side Effects (**Table G-76): Sleepiness was the most frequently reported side effects, occurring in 56 to 83 per cent. *The was a significant (P = 0.01) dose –related increase in sleepiness for increasing doses of morphine and a borderline-significant (P = 0.05) decrease in sleepiness for increasing doses of dextroamphetamine*. For sweating, the next most frequent side effect, there was no consistent morphine effect, but there was a definite dextroamphetamine effect (P = 0.01). The frequency of sweatiness rose from 17 % in patients who received morphine alone to 32% with addition of 5 or 10 mg of dextroamphetamine. This was the only side effect in which dextroamphetamine added significantly to the morphine effect.
Authors' Comments	Dextroamphetamine adds substantially to the analgesic effect of morphine while offsetting or minimizing other undesirable effects of morphine. Analgesia, as measured by the patients' subjective responses to questions about relief of pain, was augmented when dextroamphetamine was given with morphine; the combination of dextroamphetamine, 10 mg, with morphine was twice as potent as morphine alone, and the combination with 5 mg was 1½ times as potent as morphine. In simple performance tests, and in measures of side effects, dextroamphetamine generally offset undesirable effects of morphine (sedation and loss of alertness) while increasing analgesia. Effects on blood pressure, pulse and respiratory rate were minimal. Conclusion: Morphine resulted in a dose related impairment on all 3 performance measures. The impairment was counteracted by the addition of dextroamphetamine, which also appeared to enhance the analgesic effect of morphine. The combination resulted in patients being considerably more alert than they would have been with the same analgesic dose of morphine given alone.

Table G-76. Frequency of Side Effects for All Patients*

Side Effect	0 Mg of Dextro-amphetamine with Morphine			5 Mg of Dextro-amphetamine with Morphine			10 Mg of Dextro-amphetamine with Morphine		
	3 mg (48)†	6 mg (49)	12 mg (52)	3 mg (51)	6 mg (52)	12 mg (52)	3 mg (50)	6 mg (46)	12 mg (50)
		%			%			%	
Sleepiness	67	71	83	65	60	79	56	65	66
Sweatiness	25	12	14	28	29	38	30	33	32
Dizziness	8	22	23	37	17	27	20	24	22
Nausea	12	22	10	14	19	15	20	17	20
Headache	6	22	14	18	8	15	16	17	16
Vomiting	0	0	0	0	0	0	0	0	0

*Patients were questioned about the 6 effects above at each interview. In addition, the following infrequent effects were reported: other central nervous system, 0–10%; visual, 0–8%; flushed, 0–4%; & tremors, 0–6%.

†Figures in parentheses denote no. of patients.

Menefee LA, Frank ED, Crerand C, Jalali S, Park J, Sanschagrin K, Besser M. The effects of transdermal fentanyl on driving, cognitive performance, and balance in patients with chronic nonmalignant pain conditions. Pain Med 2004 Mar; 5(1):42-9.									
Key Questions Addressed	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
								X	
Research Question	To evaluate driving performance, cognition, and balance in patients with chronic non-malignant pain before and after the addition of transdermal fentanyl to their treatments.								
Drug examined	Opioids – Transdermal fentanyl and oxycodone								
Study Design	Prospective, one group-pretest-posttest design (patients acting as their own controls before and after achieving a stable dose of transdermal fentanyl)								
Population	**Inclusion Criteria**	Age = 18 to 67 yrs. Suffering from chronic nonmalignant pain, taking <15 mg of oral oxycodone per day (i.e., approximately three acetaminophen 325 mg / oxycodone 5 mg tablets). Valid driving license. Deemed appropriate for long-acting opiate therapy by their treating physicians and able to complete tests. Informed consent.							
	Exclusion Criteria	Treated with the following drugs: benzodiazepines, tizanidine, cyclobenzaprine, carisoprodol, methocarbamal, chlorzoxazone, or metaxalone, or >20 mg per day of lioresal							
		N = 23 (Does not include four patients who dropped out) Age: yrs mean ±SD (range) 47 ±10 (33-67) Sex: % male 6 (26%) Breakthrough medication Usage, mg/day (oxycodone equivalent) Before fentanyl Mean: 12 ±4 SD; On fentanyl Mean: 11 ±4 SD Pain score (VAS) Before fentanyl mean: 67±21SD; On fentanyl mean: 53 ±29 SD Final fentanyl dose, N (%) 25 µg/hour 8 (35%) 50 µg/hour 11 (48%) 75 µg/hour 4 (17%) Diagnoses Degenerative spinal conditions (N = 13) 12 (53%) Lumbar pain 1 (4%) Cervical pain Neuropathic pain (N = 10) 7 (30%) Upper extremity 3 (13%) Lower extremity							
	Generalizability to CMV drivers	Unclear							
Procedures	Patients taking less than a 15-mg equivalent of oxycodone per day took baseline driving performance, cognitive, and balance tests. Transdermal fentanyl was initiated and titrated in 25-µg/hour increments, weighing benefits and side effects. Other medications that begun prior to the study continued and did not change during the course of the study. At the end of a 1-month period, the achieved dose was maintained for another month. After they were stabilized for 1 month, patients repeated driving, cognitive, and balance tests.								
Statistical Methods	Data from this one-group pretest-posttest design were analyzed with SPSS for windows (version 9; SPSS Inc., Chicago, IL). Non parametric statistical analyses were conducted using the Wilcoxon signed rank test to assess differences between the pre- and post-test scores. SPSS uses the Z score as a standard statistic for the Wilcoxon test. The level of statistical significance was set at p <0.05.								

Quality assessment	**Internal Validity**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
		14	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
		27	**28**											

Relevant Outcomes Assessed	**1. Driving performance**. The simulator(Doron L-350, Doron Precision Systems, Inc., Binghampton, NY) was used for four driving tasks: a) Simple braking reaction time (scores were computed as an average of the middle 10 values of 14 trials). b) Cue recognition reaction time (an average was computed from eight presentations, each subsequently more difficult) c) Destination driving involved following direction during in-town and highway driving scenarios to arrive at final destination.(the final score was an average of breaking, steering, speed, and signaling errors during each of these scenarios) d) Evasive action was taking appropriate action in three critical driving situations. (The final score was the average time taken for response over the three trials. **2. Cognitive performance**: Cognitive skills tested included visual motor tracking/mental flexibility, memory and attention. Visual motor tracking/ mental flexibility were measured by the Trail Making Test A & B. Final scores were the time taken to complete each test. Memory was tested by the Rey Complex Figure Test and Recognition Trial and the Weschler Memory Scale- III Spatial Span test (WMS-III). Visual and constructional memory was tested by the Rey. Visual and spatial memory was tested by WMS-III. Attention was tested by the d2 Test of Attention and a computerized task (Conner's Continuous Performance Test II [CPT-II].) Focus and attention was tested with the d2 Test of Attention. Concentration and reaction time were with the CPT-II. **3. Balance** was tested by a physical therapist. The Berg Balance Test consists of tasks that require patients to demonstrate balance (e.g., standing with eyes closed, standing on one leg).
Results	Twenty three patients completed the study; one patient never completed forms and was excluded from the study and three discontinued secondary to side effects that did not require any treatment. Side effects included mild sedation (two patients) and itching at the site of the patch (one patient).There were no serious adverse events from the use of the fentanyl patch during the course of this study. The median dose at the end of the titration period was 50µg/hour. Self- reported pain decreased between the baseline visit (mean VAS score: 67) and the stabilization visit (mean VAS score : 53 ; Z = -2.2, P = 0.02). **Driving performance (**Table G-77): Overall, there were no differences between measures of driving before and during treatment with transdermal fentanyl. No significant differences were found between simple braking reaction time (Z = 0.34, P = 0.72) or cue recognition reaction times (Z = 0.37, P = 0.72) before and during The use of transdermal fentanyl. No differences in errors were found between in-town destination driving (Z = 1.29, P = 0.20) or highway destination driving (Z = 1.18, P = 0.24) tested before and during the use of transdermal fentanyl. Additionally, no differences were found between measures of taking evasive action (i.e., driving in critical situation) (Z = 1.06, P = 0.29) prior to and during transdermal fentanyl use. **Cognitive performance (**Table G-78**):** No decrements in cognitive performance were found. *Improvements in visual motor tracking, visual memory, and attention were found during treatment with transdermal fentanyl*. There was no decrease in performance in either Trails A or Trails B. There was no significant difference between scores on the test of visual motor tracking- Trails A (Z = 0.75, P = 0.46) and there was improvement on the test on mental flexibility- Trails B (Z = 2.19, P = 0.03) taken before and during treatment with transdermal fentanyl. Tests of visual and constructional memory revealed no difference between spatial sequences (WMS-III; Z = 0.87, P = 0.38) or recognition recall (Rey Recognition; Z = 0.88, P = 0.38) measured before and during treatment with transdermal fentanyl. Improvement was found in both immediate recall (Z = 3.88, P <0.001) AND 20-minute-delayed recall (Z = 2.75, P = 0.01) during transdermal use. There was no decrease in performance on several measures of attention after transdermal use. No differences were found in concentration (d2 Test of Attention Concentration Score; Z = 1.34, P = 0.18) or in reaction time (CPT-II Hit Reaction Time; Z = 1.64, P = 0.10) before and during treatment with transdermal fentanyl. Improvement were found in focus (d2 Test of Attention Fluctuation Score; Z = 2.89, P <0.01) and attentiveness (CPT-II Attentiveness Score; Z = 2.37, P = 0.02) while on the transdermal fentanyl. **Balance (**Table G-79**):** No significant differences were found in two tests of balance, namely, bodily sway (Z = 0.0, P = 1.0) and the Berg Balance Test (Z = 0.55, P = 0.59), between the testing periods.
Authors' Comments	The addition of trandermal fentanyl to the treatment regimen for patients with chronic nonmalignant pain conditions taking up to 15 mg oral oxycodone equivalent (i.e., approximately three tablets) per day did not negatively affect driving performance , reaction time, or cognition. Future studies in this area are needed and could provide information on making treatment decisions. There are several limitations to this study: 1. The sample was small. 2. Lack of statistical significance does not necessarily mean no differences existed, because the study was a pilot study and not powered. However, confidence intervals for the mean differences were computed by estimation through paired sample t-tests. All sample means fell within the 95% confidence intervals computed. Therefore, results revealed that the procedure was such that 95% confidence intervals obtained would include the true parameter. 3. Driving simulation was tested versus on-the-road driving. 4. The study does not address the effects of transdermal fentanyl in the time period immediately after the initiation of therapy. The question remains as to whether or not patients have difficulty driving during the initiation of treatment with transdermal fentanyl. 5. The study did not address doses of opioids higher than 75µg/hour.

Table G-77. Driving Performance Before and During Treatment with Transdermal Fentanyl

Variable	Before fentanyl Mean (SD)	On fentanyl Mean (SD)	Z value*	*P* =
Simple braking reaction time, seconds	0.090 (0.17)	0.91 (0.18)	0.34	0.74
Cue recognition reaction time, seconds	0.88 (0.17)	0.91 (0.23)	0.37	0.72
In-town driving, errors made	13.2 (4.4)	13.0 (3.6)	1.29	0.20
Highway destination driving, errors made	5.3 (2.4)	5.3 (2.8)	1.18	0.24
Evasive action reaction time, seconds	0.90 (0.03)	0.76 (0.36)	0.06	0.29

*Wilcoxon signed rank test

Table G-78. Cognitive Performance Before and During Treatment with Transdermal Fentanyl

Variable	No fentanyl Mean (SD)	On fentanyl Mean (SD)	Z value*	P value
Visual motor tracking§				
Trail making test A, seconds	36.9 (14.8)	34.0 (19.1)	0.75	0.46
Trail making test B , seconds	77.7 (29.6)	63.9 (21.3)	2.19	0.03
Visual/constructional memory¶				
Spatial sequences (WMS-III0, number correct	14.8 (3.6)	15.1 (3.8)	0.87	0.38
Recognition recall (Rey), t-score	40.8 (14.6)	43.3 (13.1)	0.88	0.38
Immediate recall (Rey), t-score	35.0 (9.7)	48.2 (13.9)	3.88	<0.01
Delayed recall (Rey), t-score				
Attention †	34.1(10.1)	42.0 (13.1)	2.57	0.01
Concentration (d2), number correct-number errors	168.7 (46.0)	171.7 (2.6)	1.34	0.18
Reaction time (CPT-II),t-score	55.2 (12.6)	57.3 (14.4)	1.64	0.10
Focus (d2), max – min raw score	13.61 (5.8)	8.8 (2.8)	2.89	<0.10
Attentiveness (CPT-II), t-score	43.9 (12.8)	39.6 (11.8)	2.37	0.02*

*Wilcoxon signed rank test. Better performance is indicated by: a lower number of seconds; ¶A higher number correct and higher t-scores; ‡ for concentration, higher number correct – number errors; for reaction time, lower-scores; for focus, lower max-min raw score; and for attentiveness, lower t-scores.

Table G-79. Bodily Sway and Balance

Variable	No fentanyl Mean (SD)	On fentanyl Mean (SD)	Z value*	P value
Bodily sway (force plate), centimeters	0.75 (0.49)	0.71 (0.43)	0.000	1.00
Balance (Berg Balance Scale), total score	52.7 (5.1)	52.6 (5.4)	0.545	0.586

*Wilcoxon signed rank test

<table>
<tr><td colspan="15">Saarialho-Kere U, Mattila MJ, Seppala T. Pentazocine and codeine: effects on human performance and mood and interactions with diazepam. Med Biol 1986; 64(5):293-9.</td></tr>
<tr><td rowspan="2">Key Questions Addressed</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td></tr>
<tr><td></td><td>X</td><td></td><td></td><td></td><td></td><td></td><td>X</td></tr>
<tr><td>Research Question</td><td colspan="14">To study the interactions between narcotics and diazepam as well as to compare the effects of pentazocine and codeine alone on objective and subjective estimates of performance</td></tr>
<tr><td>Drug examined</td><td colspan="14">Opioids–Codeine 100mg (oral)</td></tr>
<tr><td>Study Design</td><td colspan="14">Double-blind, crossover</td></tr>
<tr><td rowspan="4">Population</td><td>Inclusion Criteria</td><td colspan="13">Healthy students</td></tr>
<tr><td>Exclusion Criteria</td><td colspan="13">NR</td></tr>
<tr><td>Study population characteristics</td><td colspan="13">10 healthy students volunteers (5 males and 5 females) aged 20-26 years and weighing 58-77kg
The students were social drinkers and none of them regularly used medicines</td></tr>
<tr><td>Generalizability to CMV drivers</td><td colspan="13"></td></tr>
<tr><td>Procedures</td><td colspan="14">The subjects with no previous experience of any benzodiazepine were given 10 mg diazepam two weeks before the first session. This was done to reduce the development of behavioral tolerance to diazepam during the experimental period.
The subjects received double-blind and crossover single doses of placebo, pentazocine (75mg) and codeine (100 mg as codeine phosphate) at two weeks intervals. The treatments were randomized according to Latin Square. The tests were done 1h 30 min, 3 h, 4 h and 4h 30min after the initial drug intake. Diazepam (0.25 mg/kg) was given immediately after the test at 1h 30min. For safety, naloxone was given intravenously after the 4 h test to eliminate possible late effects of opiates.
The tests were always given in the same order.</td></tr>
<tr><td>Statistical Methods</td><td colspan="14">Mean ±SEM values were computed from the raw data separately for the absolute test performances as well as for Δ-values (changes from baseline). The latter represents responses to drugs and they were compared against respective placebo values (paired t–test; Wilcoxon test). Since the treatment sequences may modify performances and drug responses. A split-split plot ANOVA was computed for drug responses using mean variance as wall as its contributions by the subject, test week, test time, drug and their mutual relation as variables. Side–effects scored on the questionnaire were analyzed with Fisher's exact probability test.</td></tr>
<tr><td rowspan="6">Quality assessment</td><td rowspan="2">Internal Validity</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td><td>11</td><td>12</td><td>13</td></tr>
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<tr><td rowspan="2">9.2</td><td>14</td><td>15</td><td>16</td><td>17</td><td>18</td><td>19</td><td>20</td><td>21</td><td>22</td><td>23</td><td>24</td><td>25</td><td>26</td></tr>
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<tr><td rowspan="2">High Quality</td><td>27</td><td>28</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>NR</td><td>Y</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Relevant Outcomes Assessed</td><td colspan="14">Objective tests: Digit Symbol Substitution (DSST), Flicker Fusion (CFF), Body Sway on an electronic platform, Maddox Wing test and the measurement of lateral gaze nystagmus
Subjective effects were measured on visual analogue scales, (VAS): the subjects locate their position on a horizontal 100 mm ungraded line between the two extremes. The two extremes were drowsy/alert; calm/nervous; mentally slow/quick witted; hostile/friendly; sad/happy; bored/interested; discontent/content; silent/talkative; very bad performance/very good performance; lazy/effective; withdrawn/social.
The subjects also scored various psychosomatic symptoms from 0 to 3 on a 42-item questionnaire (VIGFIN) which was filled after every test-time. Blood pressure and heart rate were measured at baseline and at 3h.</td></tr>
<tr><td>Results</td><td colspan="14">Obvious learning effects was seen in the baselines of digit symbol substitution test which improved from the first to the third week (P <0.001; paired <i>t</i> test). The baseline values for the angle nystagmus showed an opposite trend, showing an impairment (decrease) with weeks (P <0.05). On the other hand, the baseline values in all VAS- assessment remained similar.
<i>Pentazocine and codeine alone filed to affect performance in objective tests</i>. With <i>regard to subjective assessments codeine tended to slow the subjects mental responses (P <0.05; t test).</i>
Combined effects of analgesic and diazepam (Table G-80): These effects can be seen from the results recorded at the 3h, 4h and 4 h 30min tests. Neither codeine nor pentazocine added significantly to the diazepam induced impairment in objective tests. When given after codeine the peak effects of diazepam on scales drowsy/alert (P <0.05, Wilcoxon test) and calm / nervous (P <0.05) appeared later than after placebo + diazepam. <i>Codeine counteracted diazepam induced feeling of impaired performance (Wilcoxon test; P <0.05</i>). Neither diazepam nor the opiates modified the variable satiated / hungry; there was a general trend towards feeling more hungry as the time passed.
Side-effects: The subjects reported side-effects such as headache, blurred vision, dry mouth, nausea, vomiting, itching, drowsiness, increased perspiration and dizziness similarly when on placebo or analgesics. This was due to the relatively strong effects of diazepam present in each group. The trend of diazepam to lower systolic blood pressure reached statistical significance when given after pentazocine and codeine (t-test; P <0.01 vs. baseline). Diastolic blood pressure and heart rate remained uninfluenced by the treatments.
Pharmacokinetics: The plasma concentration of the analgesics and diazepam are given in Table G-81. It appears that the concentrations of analgesics were low in morphine equivalents, Codeine yielded bioassayed concentrations which are comparable to</td></tr>
</table>

	those after 10 mg oral dose of morphine. When analgesics were given before diazepam the plasma diazepam levels did not peak so strongly at 3h. When analyzing the chemically assayed diazepam concentrations with two-way ANOVA (treatment x time), a significant (P <0.01) difference was found between treatments (placebo, pentazocine, codeine) but not between times. This was mainly attributable to lowered diazepam concentrations after codeine. When the same diazepam was analyzed with paired-t-test, the concentration ratio 90 min/ 3h was not significantly altered by analgesics. The latter also applies to bioassayed diazepam concentrations. Accordingly, *lowered plasma diazepam concentrations after codeine can reflect reduced rather than postponed absorption of diazepam.*
Authors' Comments	*Codeine and pentazocine alone failed to affect performance in objective tests* (body sway, DSST, CFF, Maddox wing, and nystagmus) recorded at 1h 30min. Visual analogue scale showed subjective drug effects: codeine made the volunteers mentally slow. 75mg of pentazocine and 100mg of codeine produced comparable plasma opiate activity (determined in morphine equivalents) according to radioreceptor bioassay. Impaired performance was clear at the tests done 1.5 and 2.5 h after diazepam. No major interactions were found between opiates and diazepam in objective tests with the exception that nystagmus was stronger after the combined treatments than after diazepam alone. Codeine reduced the absorption of diazepam. *Subjectively codeine and pentazocine counteract the effects of diazepam. The subjects overestimated their performance after opiates + diazepam when compared to diazepam alone.* The results suggest that no major harmful interactions on performance take place when moderate oral doses of opiates and benzodiazepines are given in combination. The lack of impairment of performance by codeine and pentazocine in the present trial disagrees with previous results obtained with intramuscular pethidine. The route of administration obviously contributes much to the effects of narcotic analgesics on performance since only occasionally have oral doses been reported as affecting psychomotor skills. In contrast to objective data, subjective parameters were affected by narcotic analgesics in the present trial. Both narcotics tended to counteract the effect of diazepam on subjective performance. *Diazepam alone gave the subjects the realistic feeling of affected capability while the opiates seemed to upset this view*. This fact could turn out to be potentially dangerous in practical situations. *The effects of codeine were sen in VAS scale bad performance / good performance*. As a mu-agonist codeine particularly, is suggested as having a prominent euphoric action.

Table G-80. Absolute Scores for Selected Tests

Test/Group	Baseline	1.5 h*	3 h**	4 h***	4.5 h
Digits substituted					
Placebo	157±8	153±7	138±7[c]	138±8[b]	140±6[c]
Pentazocine	148±6	148±6	131±7[b]	128±6[c]	134±6[b]
Codeine	156±6	151±6	133±9[c]	133±8[c]	138±7[b]
Maddox wing (d)					
Placebo	−4.9±1.0	−5.0±1.1	−6.8±1.1[a]	−7.1±1.1[a]	−6.5±1.1
Pentazocine	−4.3±0.9	−4.5±0.7	−7.1±1.1[c]	−7.3±1.1[c]	−7.4±1.2[c]
Codeine	−4.3±1.1	−4.9±1.1	−6.5±1.3[a]	−6.8±1.3[b]	−6.5±1.2[b]
Drowsy/alert (mmVAS)					
Placebo	49±7	39±5	29±6[a]	27±5[a]	38±3
Pentazocine	54±6	52±5	41±4	30±5[a]	40±4
Codeine	48±6	43±6	30±4[a]	28±3[a]	40±3
Bad/good performance (mmVAS)					
Placebo	57±6	45±5[a]	29±5[b]	27±4[c]	37±6[a]
Pentazocine	53±5	48±3	33±4[b]	35±4[b, d]	37±5[b]
Codeine	47±4	41±3	31±4[b, d]	33±3[b, d]	41±3

* diazepam was given at 1 h 45 min; ** second dose of pentazocine was given at 3 h 15 min; *** naloxone was injected at 4 h 15 min. a = $P < 0.05$, b = $P < 0.01$, c = $P < 0.001$ vs. baseline, paired *t*-test. d = $P < 0.05$ vs. placebo, paired *t*-test.

Table G-81. Mean Plasma Levels of Analgesics and Diazepam

Treatment/ Time	Analgesics ng/ml		Benzodiazepines ng/ml	
	Bioassay	GLC	Bioassay	GLC
Pentazocine				
1 h 30 min	6 ± 2	12 ± 4		
3 h	7 ± 2	25 ± 4	481 ± 92	405 ± 56
4 h 30 min	19 ± 5	39 ± 6	565 ± 109	369 ± 44
Codeine				
1 h 30 min	6 ± 1	105 ± 2		
3 h	6 ± 1	93 ± 10	412 ± 72	334 ± 68
4 h 30 min	7 ± 2	78 ± 8	434 ± 112	318 ± 51
Placebo				
3 h			598 ± 95	526 ± 111
4 h 30 min			527 ± 61	382 ± 95

Given are means ± SEM. Bioassayed concentrations of analgesics refer to ng/ml of standard morphine and bioassayed plasma benzodiazepine (diazepam + metabolites) concentrations refer to ng/ml of standard diazepam. Plasma nordiazepam levels were low (5–30 ng/ml) according to gas-liquid-chromatography (GLC).