Evidence Report

Narcolepsy (with and without Cataplexy) and Commercial Motor Vehicle Driver Safety

Presented to

The Federal Motor Carrier Safety Administration

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Evidence reports are independently reviewed by the Agency's Medical Review Board (MRB) and Medical Expert Panel (MEP).

FMCSA considers MRB recommendations, MEP opinions and other data; however, all proposed changes to current standards and guidelines will be subject to public notice and comment and relevant rulemaking processes.

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Policy Statement

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Executive Summary

Purpose of Evidence Report

According to the U.S. Department of Transportation[1] (Federal Motor Carrier Administration [FMCSA], 2009), there were 147,533 large trucks and 13,506 buses involved in fatal and non-fatal crashes in 2007. Of these, there were 86,245 and 16,237 injuries resulting from large truck and bus crashes, respectively. Similarly, 4,584 and 278 crashes for large trucks and buses, respectively, resulted in 4,808 (from trucks) and 322 (from buses) fatalities.

Numerous studies have highlighted the significant role that excessive daytime sleepiness (EDS) plays in a large number of reported crashes (FMCSA, 2009). Estimates of its contribution to accidents range from as low as 1 percent to 3 percent (Knipling & Wang, 1995; U.S. Department of Transportation [DOT], National Center for Statistics and Analysis, 1998) to as high as 35 percent to 42 percent (Dingus et al., 1987; Leger, 1994), and it has been suggested that sleepiness is second only to alcohol as the most frequent cause of both single and multiple motor-vehicle accidents (Dingus et al., 1987).

Besides sleep apnea, the main clinical disorder characterized by EDS is narcolepsy. Narcolepsy is a neurological disorder affecting the regulation of sleep and wakefulness. It is characterized by EDS, cataplexy, and other rapid eye movement (REM) sleep-associated manifestations (e.g., hypnagogic hallucinations and sleep paralysis). Narcolepsy is distinct from most other sleep disorders because the primary symptom (i.e., EDS) is not due to disturbed nocturnal sleep or misaligned circadian rhythms.

The purpose of this evidence report is to address several questions posed by FMCSA regarding the topic of narcolepsy and commercial motor vehicle (CMV) driver safety. In the early scope development work conducted by the Agency and the Medical Review Board (MRB), the following issues of concern were raised:

1. Does narcolepsy result in an increased risk of CMV crash? Does narcolepsy result in an increased risk of personal vehicle crash?
2. Is there experimental evidence that narcolepsy results in driving impairment (e.g., driving simulator studies)?
3. Is there quality evidence that treatment of narcolepsy reduces risk of crash to that of the appropriately certified CMV driving population? Is there quality evidence that treatment of narcolepsy reduces risk of personal vehicle crashes to that of the healthy general driving population?
4. Does use of modafinil to treat narcolepsy reduce risk of crash to that of the appropriately certified CMV driving population? Does use of modafinil for treatment of narcolepsy reduce risk of personal vehicle crash to that of the healthy general driving population?

[1]These statistics are derived from two sources: the Fatality Analysis Reporting System (FARS) and the Motor Carrier Management Information System (MCMIS): http://ai.fmcsa.dot.gov/CrashProfile/n_overview.asp .

The specific key questions of the Agency and the MRB were reframed for the purpose of the evidence report, as follows:

Key Question 1: Are individuals with narcolepsy (with or without cataplexy) at an increased risk for a motor vehicle crash when compared to comparable individuals without the disorder?

Outcomes assessed are the following:

- Crash risk (CMV and private license holders)
- Driving performance (simulated or observed).

Key Question 2: Do currently recommended treatments for narcolepsy reduce the risk for a motor vehicle crash?

Outcomes assessed are the following:

- Crash risk (CMV and private license holders)
- Simulated driving performance.
- Cataplexy
- Measures of cognitive and psychomotor function

Identification of Evidence Bases

Separate evidence bases for each of the key questions addressed by this evidence report were identified using a process consisting of a comprehensive search of the literature, examination of abstracts of identified studies in order to determine which articles would be retrieved, and the selection of the actual articles that would be included in each evidence base.

Electronic searches of PubMed and the Transportation Research Information Services (TRIS) databases were conducted (through July 2009). 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 the "gray literature" were also performed. Admission of an article into an evidence base was determined by formal retrieval and inclusion criteria that were determined *a priori.*

Grading the Strength of Evidence

Our assessment of the quality of the evidence took into account not only the quality of the individual studies that compose the evidence base for each key question; we also considered the interplay between the quality, quantity, robustness, and consistency of the overall body of evidence.

Analytic Methods

The set of analytic techniques used in this evidence report was extensive. When appropriate, random-effects meta-analyses were used to pool data from different studies. Differences in the findings of studies (heterogeneity) were identified using the Q-statistic and I^2. Sensitivity analyses, aimed at testing the robustness of our findings, included separate removal and replacement of each individual study.

Presentation of Findings

In presenting our findings, we made a clear distinction between qualitative and quantitative conclusions and we assigned a separate "strength of evidence" rating to each conclusion format. The strength of evidence ratings assigned to these different conclusions is defined in Table 1.

Table 1: 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.
Minimally acceptable	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.
Insufficient	Although some evidence exists, the evidence is insufficient to warrant drawing an evidence-based conclusion.
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 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.
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.
Unstable	Estimates of the treatment effect are too unstable to allow a quantitative conclusion to be drawn at this time.

Evidence-Based Conclusions

Key Question 1: Are individuals with narcolepsy (with or without cataplexy) at an increased risk for a motor vehicle crash when compared to comparable individuals without the disorder?

Currently available evidence (both direct and indirect) supports the contention that drivers with narcolepsy are at an increased risk for a motor vehicle crash when compared to otherwise similar individuals who do not have the disorder (Strength of Evidence: Strong).

- **The estimated magnitude of increased risk is RR (Risk Ratio) = 6.15 (95% CI: 3.50, 10.78) (Stability of Evidence: Moderate).**

Direct Evidence – Crash Studies: Current direct evidence from three crash studies (Quality Rating: "Low") conducted with non-CMV drivers showed that individuals with narcolepsy are at an increased risk for a crash compared to individuals who do not have narcolepsy. Meta-analytic pooling of these data revealed that the estimated risk of crash associated with narcolepsy is RR = 6.15 (95% CI: 3.50, 10.78),

representing a six-fold increase in risk when compared to individuals without the disorder. Sensitivity analyses showed that these findings were robust. The data were qualitatively consistent and the effect size was large, making it unlikely that future studies will overturn this finding.

Indirect Evidence – Studies of Driving Tests and Driving Simulation: Five studies (Quality Rating: "Moderate") examined factors associated with simulated driving outcomes. Four of these studies examined rates of obstacles hit during a driving simulation test. These studies provided enough data to calculate effect size estimates and conduct a meta-analysis. Pooling of these data revealed that individuals with narcolepsy have higher rates of driving simulator crashes compared to individuals without narcolepsy (standardized mean difference = 0.998; 95% CI: 0.56, 1.44; p= 0.000). A standardized mean difference of 0.998 is a large effect size. Sensitivity analyses found that these findings were robust.

Two studies examined other measures of simulated driving performance, namely tracking error, number of correct responses, response time, number of out of bounds and number of concentration lapses. Findings indicated that individuals with narcolepsy had significantly more tracking error, fewer correct responses, and more instances of going out of bounds compared to healthy controls. No significant differences were found between the groups for mean response time or number of concentration lapses.

In summary, while there are limitations in the quality of the studies that examined direct crash risk in this evidence base, all study results showed a strong effect size and statistical significance. Further, indirect evidence of crash is also reported and provides strong support for the direct crash study findings. Based upon available information, there is strong evidence that non-commercial drivers with narcolepsy are at an increased risk of crash.

Key Question 2: Do currently recommended treatments for narcolepsy reduce the risk for a motor vehicle crash?

Having established that individuals with narcolepsy are at an increased risk for a motor vehicle crash we next addressed the issue of whether individuals who receive treatment for the disorder might be considered safe to drive.

According to clinical practice guidelines from the American Academy of Sleep Medicine (AASM; Morgenthaler et al., 2007) and the European Federation of Neurological Societies (EFNS; Billiard et al., 2006), the first-line of treatment for EDS and irresistible episodes of sleep associated with narcolepsy is modafinil. The second line pharmacological treatment recommended by both groups is methylphenidate at a daily dosage of 10–60 mg. In addition, AASM also recommends amphetamine, methamphetamine, or dextroamphetamine as alternative second line treatments. For cataplexy associated with narcolepsy, both professional bodies recommend sodium oxybate at a starting dose of 4.5 g/night divided into two equal doses of 2.25 g/night as the first line of treatment. However, in the U.S., sodium oxybate is also considered a first line treatment for EDS and disrupted sleep due to narcolepsy, as well as for the treatment of hypnagogic hallucinations and sleep paralysis.

In addition to modafinil and sodium oxybate, a number of other compounds are used to a limited degree when these treatments fail to improve symptoms. For instance, tricyclic antidepressants (such as

clomipramine), selective serotonin reuptake inhibitors (SSRIs; such as fluvoxamine and femoxetine), and selective norepinephrine reuptake inhibitors (SNRI; such as venlafaxine, and reboxetine) are sometimes used for the treatment of cataplexy, sleep paralysis and hypnagogic hallucinations. Similarly, selegiline (a monoamine oxidase-B [MAO-B] inhibitor) and ritanserin (a serotonin antagonist) have been used for the treatment of EDS.

For the purpose of this evidence report, each of the primary treatment options currently recommended for the treatment of narcolepsy (with or without cataplexy) are addressed as subquestions of Key Question 2. Specifically, they are:

Key Question 2A: What is the Impact of Treatment with Modafinil or Armodafinil for Narcolepsy on Driver Safety?

Key Question 2B: What is the Impact of Treatment with Sodium Oxybate for Narcolepsy on Driver Safety?

Key Question 2C: What is the Impact of Treatment with Antidepressants for Narcolepsy on Driver Safety?

Key Question 2D: What is the Impact of Treatment with Amphetamine, Methylphenidate, and Other Stimulants for Narcolepsy on Driver Safety?

Table 2 presents a summary of our findings regarding the impact of the four main treatment options for narcolepsy (i.e., modafinil or armodafinil, sodium oxybate, antidepressants, and stimulants) on crash risk. Because clinical trials of treatment efficacy are unlikely to focus on crash rates or driver performance, we determined *a priori* to expand the list of outcomes of interest to include several other outcomes. These outcomes included measures of EDS, cataplexy event rate, and measures of cognitive and psychomotor function. All three of these outcomes may be considered as surrogate markers of driving performance and crash risk. The presence of EDS and reduced cognitive and/or psychomotor function are both known to be associated with reduced driving performance and an increased risk for a motor vehicle crash. The occurrence of cataplexy while driving is an incapacitating event that is detrimental to driving performance and is a clear risk factor for a motor vehicle crash.

Table 2: Summary of Findings: Impact of Treatment

Drug	Modafinil or armodafinil					Sodium Oxybate					Antidepressants					Amphetamine, methylphenidate and other stimulants				
Outcome	Crash Risk	Driving Performance	Cataplexy	EDS	Cognitive and psychomotor performance	Crash Risk	Driving Performance	Cataplexy	EDS	Cognitive and psychomotor performance	Crash Risk	Driving Performance	Cataplexy	EDS	Cognitive and psychomotor performance	Crash Risk	Driving Performance	Cataplexy	EDS	Cognitive and psychomotor performance
Number of Studies	0	0	0	12	3	0	0	2	3	0	0	0	8	8	1	0	1	1	3	1
Effective in reducing symptom?	?	?	NA	◎	◎	?	?	◎	◎	?	?	?	?	?	?	?	?	?	◎	?
Effective in normalizing symptom?	?	?	NA	◎	◎	?	?	◎	◎	?	?	?	?	?	?	?	?	?	◎	?

◎ Yes

◎ No in vast majority of cases (≤20%)

NA Not Applicable

? No evidence-based conclusion drawn

Key Question 2A: What is the Impact of Treatment with Modafinil and Armodafinil for Narcolepsy on Driver Safety?

Direct Evidence – Crash Studies:

- **Evidence-based conclusions pertaining to the impact of treatment with modafinil or armodafinil on crash risk among individuals with narcolepsy cannot be drawn at this time.**

No studies that directly examined the impact of treatment with modafinil or armodafinil on crash risk were identified by our searches.

Indirect Evidence: Driving Performance (Simulated or Closed Course) Studies, Studies of Symptoms Associated with Crash Risk:

- **Evidence-based conclusions pertaining to the impact of treatment with modafinil or armodafinil on driving performance among individuals with narcolepsy cannot be drawn at this time.**

No studies that examined the impact of treatment with modafinil or armodafinil on driving performance were identified by our searches.

- **Modafinil and armodafinil are effective in improving symptoms of EDS (as measured using Epworth Sleepiness Scale [ESS] scores and sleep latencies for the Mean Sleep Latency Test [MSLT] and Maintenance of Wakefulness Test [MWT]) in patients with narcolepsy. However, improvements do not attain normal levels in the majority of patients (Strength of Evidence: Strong).**

Twelve studies evaluated outcomes related to daytime sleepiness in patients with narcolepsy (both with and without cataplexy). Ten studies (Quality Rating: one "Low", three "Moderate", and six "High") assessed the use of modafinil (or armodafinil) on ESS scores. In all 10 studies, ESS scores were improved. Post treatment scores were typically between 11 and 14.

Ten studies (Quality Rating: one "Low", two "Moderate", and seven "High") also examine the efficacy of modafinil (or armodafinil) on sleep latency measured with either the MSLT and/or the MWT. Again, in all cases, latencies were improved following treatment with modafinil (or armodafinil). In addition, in studies that examined dose responses, there was clear evidence of a dose-dependent response. However, on average, latencies did not reach normal values.

In summary, there is clear and robust evidence that treatment with modafinil or armodafinil is effective in reducing daytime sleepiness associated with narcolepsy; however, the majority of patients do not reach normal levels.

- **Evidence-based conclusions pertaining to the impact of treatment with modafinil or armodafinil on cognitive and psychomotor performance among individuals with narcolepsy cannot be drawn at this time.**

Currently available evidence is mixed with respect to the impact of modafinil on cognitive factors. Three studies (Quality Rating: "High") examined cognitive function (using variable measures) of patients treated with modafinil. In two studies that used the Four Choice Reaction Time Test (FCRTT), no evidence of improvement was evident following treatment with modafinil. However, one study showed significant reductions in errors on the Wisconsin Card Sort Test (WCST).

Key Question 2B: What is the Impact of Treatment with Sodium Oxybate for Narcolepsy on Driver Safety?

Direct Evidence – Crash Studies:

- **Evidence-based conclusions pertaining to the impact of treatment with sodium oxybate on crash risk among individuals with narcolepsy cannot be drawn at this time.**

No studies that directly examined the impact of treatment with sodium oxybate on crash risk were identified by our searches.

Indirect Evidence: Driving Performance (Simulated or Closed Course) Studies, or Studies of Symptoms Associated with Crash Risk:

- **Evidence-based conclusions pertaining to the impact of treatment with sodium oxybate on driving performance among individuals with narcolepsy cannot be drawn at this time.**

No studies that directly examined the impact of treatment with sodium oxybate on driving performance were identified by our searches.

- **Currently available evidence suggests that sodium oxybate is effective in improving self-reported symptoms of cataplexy in individuals with narcolepsy. However, treatment with the drug does not eliminate cataplexy entirely in the vast majority of patients (Strength of Evidence: High).**

Two studies (Quality Rating: "High") identified by our searches examined the efficacy of sodium oxybate in reducing cataplexy in patients with narcolepsy. Significant dose-dependent reductions in the median number of cataplectic attacks were observed in both trials compared with placebo and/or baseline. However, none of the studies found that sodium oxybate eliminated cataplexy entirely in the vast majority of treated individuals.

- **Currently available evidence suggests that sodium oxybate is effective in improving symptoms of EDS in individuals with narcolepsy. However, these improvements do**

not result in levels of daytime sleepiness that can be considered to be normal in the vast majority of individuals (Strength of Evidence: High).

Three studies (Quality Rating: "High") examined the efficacy of sodium oxybate in treating EDS. Each of the three studies showed evidence of improvement on all measures of daytime sleepiness (e.g., ESS, and latencies for the MWT) compared either with placebo treated groups, or baseline values (two of which demonstrated dose-dependent improvements). However, in most studies, values did not reach normal values.

- **Evidence-based conclusions pertaining to the impact of treatment with sodium oxybate on cognitive and psychomotor function among individuals with narcolepsy cannot be drawn at this time.**

No studies that directly examined the impact of treatment with sodium oxybate on cognitive or psychomotor function were identified by our searches.

Key Question 2C: What is the Impact of Treatment with Antidepressants for Narcolepsy on Driver Safety?

Direct Evidence – Crash Studies:

- **Evidence-based conclusions pertaining to the impact of treatment with antidepressants on crash risk among individuals with narcolepsy cannot be drawn at this time.**

No studies that directly examined the impact of treatment with antidepressants for narcolepsy on crash risk were identified by our searches.

Indirect Evidence: Driving Performance (Simulated or Closed Course) Studies, Studies of Symptoms Associated with Crash Risk:

- **Evidence-based conclusions pertaining to the impact of treatment with antidepressants on driving performance among individuals with narcolepsy cannot be drawn at this time.**

No studies that directly examined the impact of with antidepressants for narcolepsy on driving performance were identified by our searches.

- **Evidence-based conclusions pertaining to the impact of treatment with antidepressants on cataplexy events among individuals with narcolepsy cannot be drawn at this time.**

Eight studies examined the impact of antidepressants on the frequency of cataplexy symptoms. Decreases in self-reported attacks of cataplexy were observed for some but not all of the antidepressants considered. For instance three studies (Quality Rating: two "high," one "Low")

found dose-dependent reductions in cataplexy with the use of selegiline while two other studies (Quality Rating: "High") using ritanserin showed no improvements in symptoms of cataplexy. Three other studies (Quality Rating: one "Low," one "Moderate," one "High") looked at the impact of tricyclic antidepressants (clomipramine), SSRIs (femoxetine), or SNRIs (viloxazine) on self-reported cataplexy. Each of these studies demonstrated significant improvements in reports of cataplexy for patients under the respective treatments. However, when improvements were demonstrated, they did not reach normal levels.

- **Evidence-based conclusions pertaining to the impact of treatment with antidepressants on measures of daytime sleepiness among individuals with narcolepsy cannot be drawn at this time.**

Eight studies examined the impact of antidepressants on measures of daytime sleepiness associated with narcolepsy. Of these, three examined the use of selegiline (Quality Rating: two "high," one "Low") on measures of daytime sleepiness. Selegiline produced dose-dependent improvements in self-reported sleepiness (measured by survey). Similarly, selegiline produced dose-dependent improvements sleep latencies on the MWT and/or MSLT reaching significance only at the highest doses (20 mg and 40 mg). Two high quality studies of the impact of ritanserin showed mixed results on improving subjective reports of daytime sleepiness, and demonstrated no improvements on measures of sleep latencies. In three other studies (Quality Rating: one "Low," one "Moderate," one "High") the antidepressants assessed (i.e., clomipramine, femoxetine, and viloxazine) demonstrated little or no improvement for any measures of daytime sleepiness. When improvements were demonstrated for any of the antidepressants assessed, they did not reach normal levels.

- **Evidence-based conclusions pertaining to the impact of treatment with antidepressants on cognitive and psychomotor function among individuals with narcolepsy cannot be drawn at this time.**

A single study (Quality Rating: "Low") assessed a measure of cognitive function (Wilkinson Addition Test [WAT]) and found no significant improvements.

Key Question 2D: What is the Impact of Treatment with Amphetamine, Methylphenidate, and Other Stimulants for Narcolepsy on Driver Safety?

Direct Evidence: Crash Studies:

- **Evidence-based conclusions pertaining to the impact of treatment with amphetamines, methylphenidate, or other related drugs on crash risk among individuals with narcolepsy cannot be drawn at this time.**

No studies that directly examined the impact of treatment with amphetamines, methylphenidate, or other stimulant drugs for narcolepsy on crash risk were identified by our searches.

Indirect Evidence: Driving Performance (Simulated or Closed Course) Studies, Studies of Symptoms Associated with Crash Risk:

- **Evidence-based conclusions pertaining to the impact of treatment with amphetamines, methylphenidate, or other related stimulant drugs on driving performance among individuals with narcolepsy cannot be drawn at this time.**

A single study (Quality Rating: "Moderate") assessed simulated driving performance of patients with narcolepsy treated with variable doses of methamphetamine. The percent of objects hit on the Steer Clear driving simulator test decreased significantly in a dose-dependent manner following treatment with methamphetamine. While the evidence suggests that methamphetamine improves simulated driving performance, the number of narcolepsy patients included in this study was quite small (n=eight). Additional evidence that replicates these findings in a larger number of individuals with narcolepsy is needed to make an evidence-based conclusion.

- **Currently available evidence suggests that amphetamines and/or methylphenidate are effective in improving symptoms of EDS in individuals with narcolepsy. However, these improvements do not result in levels of daytime sleepiness that can be considered to be normal in the vast majority of individuals (Strength of Evidence: Low to Moderate).**

Three studies (Quality Rating: one "Moderate," two "Low") examined the efficacy of amphetamines and/or methylphenidate in treating EDS. All three studies provided evidence of improvement on all measures of daytime sleepiness (e.g., ESS, and latencies for the MWT and MSLT) compared either with placebo treated groups, or baseline values. In each case the effects were dose-dependent, reaching normal levels at the highest doses.

- **Evidence-based conclusions pertaining to the impact of treatment with amphetamines, methylphenidate, or other related stimulant drugs on cataplexy events among individuals with narcolepsy cannot be drawn at this time.**

A single study (Quality Rating: "Low") assessed the impact of dextroamphetamine, mazindol, and fencamfamin on self-reported attacks of cataplexy. No improvements were demonstrated for any of these drugs on self-reported cataplexy attacks.

- **Evidence-based conclusions pertaining to the impact of treatment with amphetamines, methylphenidate, or other related stimulant drugs on cognitive and psychomotor function among individuals with narcolepsy cannot be drawn at this time.**

A single study (Quality Rating: "Low") assessed this outcome measure. Treatment of narcolepsy patients with methylphenidate resulted in dose-dependent improvements on both the WAT and the Digit Symbol Substitution (DSS) tests. Relative to normal control subjects, however,

narcolepsy patients did not achieve normal levels, even at the highest doses of methylphenidate. The number of subjects included in this study was very small. Additional evidence that replicates these findings in a larger number of individuals with narcolepsy is needed to make an evidence-based conclusion.

Preface

Organization of Report

This evidence report contains four major sections: 1) *Background*, 2) *Crash Statistics, Sleep-related Crash Data, and Relevant Regulations*, 3) *Methods*, and 4) *Evidence Synthesis*. These major sections are supplemented by extensive use of appendices.

The *Background* section summarizes basic information on the condition of narcolepsy, with and without cataplexy. In the section titled *Crash Statistics, Sleep-related Crash Data, and Relevant Regulations*, we provide information pertaining to current regulatory standards and guidelines from the FMCSA and three other government transportation safety agencies; the Federal Aviation Administration (FAA), the Federal Railroads Administration (FRA), and the Maritime Administration (MARAD). In addition, we summarize equivalent information from other countries that are generally considered to have well-developed medical fitness programs. 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 synthesis of clinical study results. The *Evidence Synthesis* 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 available data extracted from included studies either qualitatively or, when the data permit, qualitatively and quantitatively (using meta-analysis). Each section in the *Evidence Synthesis* section closes with our conclusions that are based on our assessment of the available evidence.

Scope

Commercial driving is a hazardous occupation. The trucking industry has the third highest fatality rate of all occupations (12 percent) in the United States. About two-thirds of fatally injured truck workers were involved in highway crashes. According to the DOT, of the 41,059 people killed in motor vehicle crashes in 2007, 12 percent (4,808) died in crashes that involved a large truck. Another 101,000 people were injured in crashes involving large trucks. Only about 17 percent of those killed and 22 percent of those injured in large truck crashes were occupants of large trucks.

The purpose of this evidence report is to address several key questions posed by the Agency. Each of these key questions was carefully formulated such that its answer will provide information to the Agency necessary for the process of updating its current medical examination guidelines. The key questions addressed in this evidence report are as follows:

<u>Key Question 1</u>: Are individuals with narcolepsy (with or without cataplexy) at an increased risk for a motor vehicle crash when compared to comparable individuals without the disorder?

Outcomes to be assessed are the following:

- Crash risk (CMV and private license holders)
- Driving performance (simulated or observed).

<u>Key Question 2</u>: Do currently recommended treatments for narcolepsy reduce the risk for a motor vehicle crash?

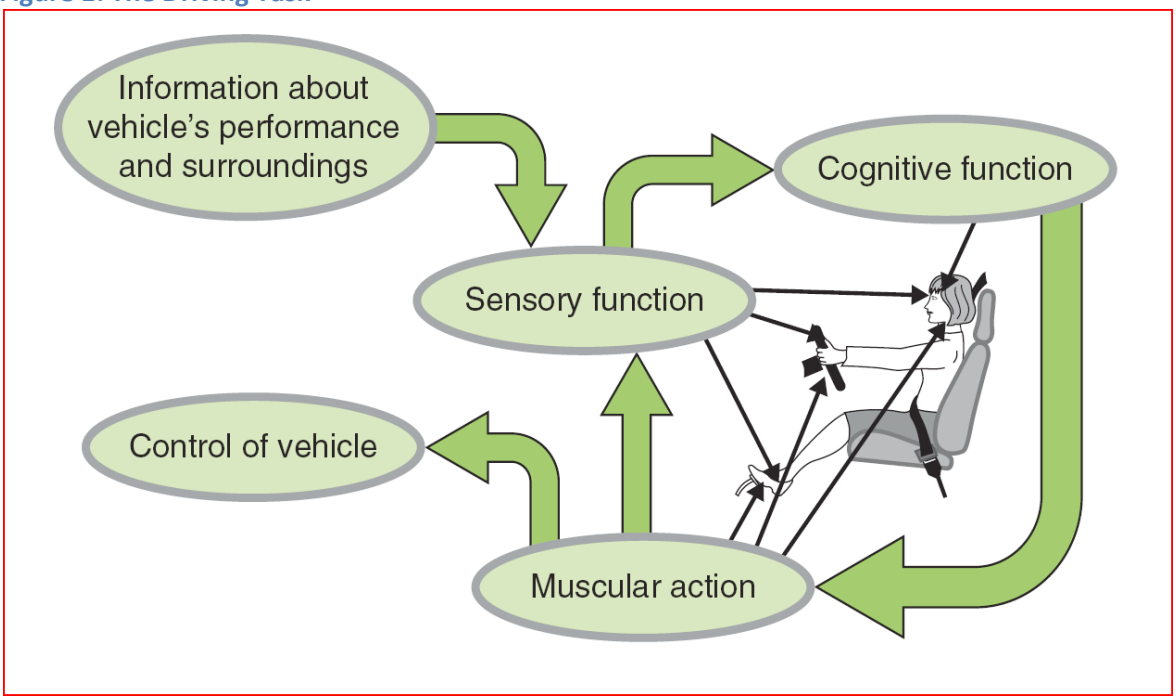
Outcomes to be assessed are the following:

- Crash risk (CMV and private license holders)
- Simulated driving performance.
- Cataplexy
- Measures of cognitive and psychomotor function

Background

Driving is a complicated activity that depends on fine coordination between the sensory and motor systems (Figure 1). The task is influenced by many different factors such as arousal, perception, attention, concentration, emotion, reflex speed, time estimation, auditory and visual functions, decision-making, and personality. Safe driving requires skills to maintain effective and reliable control of vehicles, the capacity to respond to the road, traffic, and other external clues, and the ability to follow the "rules of the road." Any condition or lowered state-of-arousal that interferes with perception, cognition (including alertness, attention, and recall), or motor function, has the potential to interfere with driving ability.

Figure 1: The Driving Task



Source: Carter, 2006 (see: http://www.dft.gov.uk/pgr/roadsafety/drs/fitnesstodrive/fitnesstodrive)

Excessive drowsiness and/or falling asleep at the wheel have been identified in numerous reports as primary factors in injurious and fatal crashes caused by both passenger and CMV drivers (FMCSA, 2009). EDS may reflect poor sleep hygiene and insufficient nocturnal sleep, or present as a symptom of a sleep disorder. Neurological illnesses such as Parkinson's disease or head trauma may also impact daytime alertness but the most severe cases of daytime somnolence are found in patients affected by narcolepsy. The purpose of this report is to summarize literature that is available on the topic of narcolepsy and driver safety.

Normal Sleep, Disruptions to Sleep, and Circadian Rhythms

Sleep is defined as a state of unconsciousness from which a person can be aroused. Sleep affects physical and mental health, and is essential for the normal functioning of all the systems of the

body. Many studies have found that sleep disorders have a deleterious impact on not only a person's body systems, but also their basic daily function. With decreased sleep, higher-order cognitive tasks are impaired early and disproportionately. On tasks used for testing coordination, sleep-deprived people often perform as poorly as, or worse than people who are intoxicated.

In general, the symptoms or effects of sleep disorders cause impaired performance, such as:

- Loss of attentiveness;
- Slower reaction times;
- Impaired judgment;
- Poor performance on skill-control tasks;
- Increasing probability of falling asleep;
- Subjective feelings of drowsiness or tiredness.

Stages of Sleep

During sleep, people usually pass through five phases: Sleep Stages 1, 2, 3, 4, and finally REM sleep (defined in Box 1). These stages progress in a cycle from Stage 1 to REM sleep, then the cycle starts over again with Stage 1. Almost 50 percent of total sleep time is spent in Stage 2 sleep, about 20 percent in REM sleep, and the remaining 30 percent in the other three stages.

Box 1: Stages of Sleep

- **Stage 1 sleep**: Occurs while a person is falling asleep. It represents about 5 percent of a normal adult's sleep time.
- **Stage 2 sleep**: In this stage, (the beginning of "true" sleep), the person's electroencephalogram (EEG) will show distinctive wave forms called sleep spindles and K complexes. About 50 percent of sleep time is Stage 2 sleep.
- **Stages 3 and 4 sleep**: Also called delta or slow wave sleep, these are the deepest levels of human sleep and represent 10-20 percent of sleep time. They usually occur during the first 30-50 percent of the sleeping period.
- **REM sleep**: REM sleep accounts for 20-25 percent of total sleep time. It usually begins about 90 minutes after the person falls asleep, an important measure called REM latency. It alternates with non-REM sleep about every 70 to 90 minutes throughout the night. REM periods increase in length over the course of the night.

During Stage 1 sleep, a person can drift in and out of sleep and be awakened easily. The eyes move very slowly and muscle activity slows. People awakened from Stage 1 sleep often remember fragmented visual images. Many also experience sudden muscle contractions, called *hypnic myoclonia*, which may be preceded by a sensation of starting to fall.

In Stage 2 sleep, eye-movements stop and electrical activity in the brain slows, with occasional bursts of rapid waves called *sleep spindles.*

In Stage 3, extremely slow brain activity (i.e., *delta waves) occurs*, interspersed with smaller, faster waves.

By stage 4, the brain produces delta waves almost exclusively. It is very difficult to wake someone during stages 3 and 4, which together are called *deep sleep.* There is no eye movement or muscle activity. People awakened during deep sleep do not adjust immediately and often feel groggy and disoriented for several minutes after they wake up.

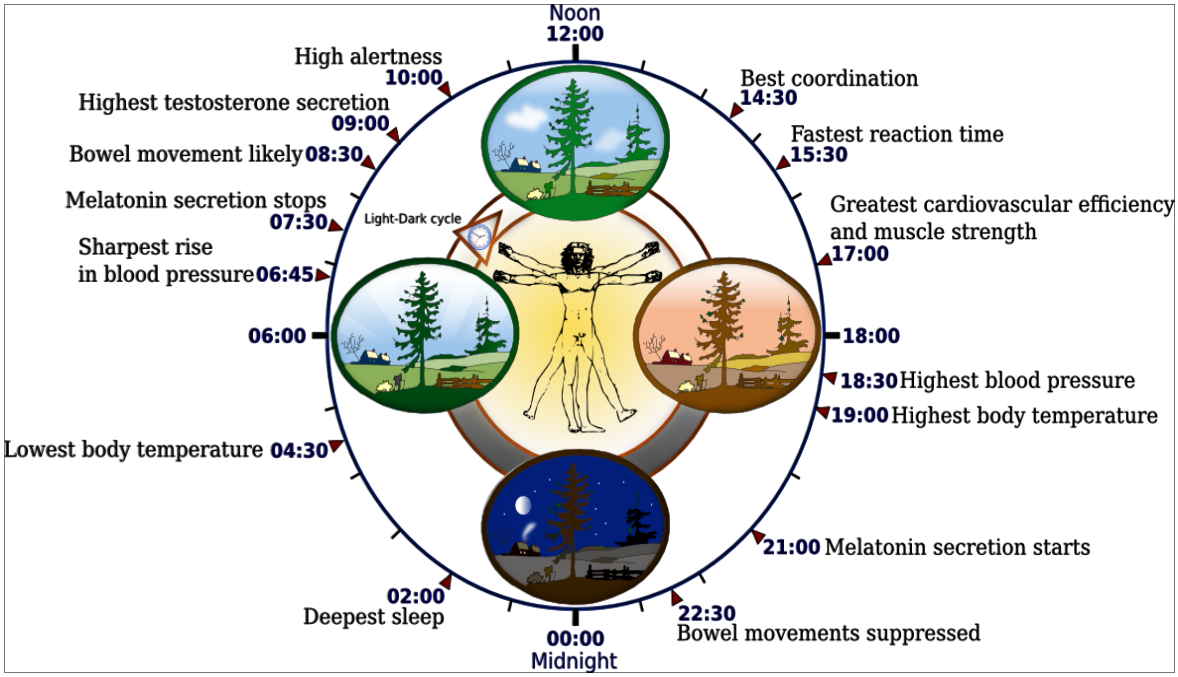
When people switch into REM sleep, their breathing becomes more rapid, irregular, and shallow, their eyes jerk rapidly in various directions, and the muscles in their limbs become temporarily paralyzed. Their heart rate increases and blood pressure rises. When people awaken during REM sleep, they often remember their dreams.

The first REM sleep period usually occurs about 70 to 90 minutes after falling asleep. A complete sleep cycle takes 90 to 110 minutes on average. The first sleep cycles each night contain relatively short REM periods and long periods of deep sleep. Near the end of sleep, the sleep cycle is comprised largely of stages 1, 2, and REM.

Circadian Rhythm

Biological variations that occur in the course of 24 hours are called circadian rhythms. Circadian rhythms are controlled by the body's biological clock (Figure 2). Many bodily functions follow the biologic clock, but sleep and wakefulness comprise the most important circadian rhythm. Circadian sleep rhythm is one of the several body rhythms modulated by the hypothalamus.

Figure 2: Overview of Biological Circadian Clock in Humans



Source: Mrabet (2004)

Individuals who have a conventional sleep pattern (sleeping for seven or eight hours overnight) experience maximum sleepiness in the early hours of the morning and a smaller dip in the early

afternoon. During the low points of the cycle, individuals have a reduced attentiveness. Similarly, people find it difficult to fall asleep during high-attentiveness periods.

Circadian rhythms can be affected to a certain degree by almost any kind of external stimulus, for example, the beeping of the alarm clock or the timing of meals. The cycle is anchored in large part by the natural sunlight and darkness cycle, but is also tied to an individual's externally imposed pattern of sleep and waking times.

Symptoms similar to those seen in people with jet lag (e.g., EDS) are common in people who work during nights or work in shifts. Because these people's wake time conflicts with powerful sleep-regulating cues like sunlight, they often become uncontrollably drowsy during work or may have difficulty falling asleep during their off time. As such, it follows that the performance of night shift workers is somewhat reduced.

In addition, circadian rhythms are persistent, and can only be shifted by one to two hours forward or backward per day by externally imposed changes in work/sleep routines and travel across time zones. Thus, changing the starting time of a work shift by more than these amounts, or the first night shift after a "weekend" break during which conventional sleep times are often followed will also reduce attentiveness. Because the function of sleep has not been fully determined, the exact number of hours that a person should sleep is unknown. Some persons claim to work optimally with only three to five hours of sleep per night, while some admit needing at least eight hours of sleep per night (or more) to perform effectively. Therefore, sleep deprivation is best defined by group means and in terms of the tasks impaired.

In tasks requiring judgment, increasingly risky behaviors emerge because the total sleep duration is limited to five hours per night. The high cost of an action is seemingly ignored as the sleep-deprived person focuses on limited benefits. These findings can be explained by the fact that metabolism in the prefrontal and parietal associational areas of the brain decrease in individuals deprived of sleep for 24 hours. These areas of the brain are important for judgment, impulse control, attention, and visual association.

Narcolepsy

Narcolepsy is a chronic neurological sleep disorder, characterized by EDS and sudden attacks of sleep. When the urge to sleep becomes overwhelming, individuals with narcolepsy will fall asleep for periods lasting from a few seconds to several minutes. In rare cases, some individuals may remain asleep for an hour or longer. These sudden sleep attacks may occur during any type of activity, at any time of the day.

In addition to EDS, three other major symptoms frequently characterize narcolepsy: cataplexy (the sudden loss of voluntary muscle tone), vivid hallucinations during sleep onset or upon awakening, and brief episodes of total paralysis at the beginning or end of sleep.

Of more than 80 types of sleep disorder diagnoses, listed in the most comprehensive classification of sleep disorders, the Second Edition of the International Classification of Sleep Disorders (ICSD-2) [AASM, 2005]) five are classified as a form of narcolepsy. These five classifications fall within two main types:

- **Narcolepsy With Cataplexy:** A sleep disorder characterized by severe, irresistible daytime sleepiness as well as the sudden loss of muscle tone (cataplexy). Sleep-onset or sleep-offset paralysis and hallucinations, frequent movement and awakening during sleep, and weight gain may be present.
- **Narcolepsy Without Cataplexy:** A sleep disorder characterized by EDS, typically associated with naps that are refreshing in nature while nocturnal sleep is normal or moderately disturbed without excessive amounts of sleep. Sleep paralysis, hypnagogic hallucinations (i.e., episodes of seeing and hearing things that are often frightening as one is falling asleep), or automatic behavior may be present.

Each type of narcolepsy is classified as a Hypersomnia of Central Origin Not Due to a Circadian Rhythm Sleep Disorder, Sleep Related Breathing Disorder or Other Causes of Disturbed Nocturnal Sleep – one of eight classifications identified in the ICSD-2.

Although not reviewed in this report, the ICSD-2 lists 10 additional types of hypersomnia of central origin, all of which are characterized by EDS. Those conditions are highlighted in Appendix A, which also offers a synopsis of the ICSD-2 classification system.

Causes of Narcolepsy

The exact cause of narcolepsy, a neurological sleep disorder, is unknown (Gross, 2006). However, it seems likely to be the consequence of a number of genetic abnormalities that affect specific biologic factors in the brain, coupled with environmental triggers, such as a virus. Researchers are currently attempting to develop a unifying theory involving genetic factors, autoimmunity, and deficiencies in hypocretin, a brain peptide that is important in regulating sleep. Most of the research conducted on narcolepsy uses dogs that have genetic factors that cause narcolepsy, and such studies are helping researchers find the biologic bases to the condition.

It has been theorized that narcolepsy may be an autoimmune disease, in which the immune system may be tricked into perceiving its own proteins to be antigens, foreign substances targeted for attack by immune factors in the body. Other Important autoimmune diseases include multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and type-1 diabetes. In such diseases, the immune system overproduces potent factors called cytokines, which cause inflammation and injury in the susceptible cells and tissues affected by the disease. Most autoimmune diseases also tend to afflict those with particular genetically determined molecules of the immune system called human leukocyte antigens (HLAs).

Some research suggests that an immune attack in narcolepsy may occur against cells containing the brain peptide hypocretin (orexin), resulting in deficiencies that are now believed to be major components of the narcolepsy process. HLAs, particularly a subgroup known as DQB1-0602, have been strongly associated with narcolepsy and low levels of hypocretin. Narcolepsy patients who carry this HLA group tend to have a specific syndrome of symptoms that include cataplexy and periodic limb movement disorder. However, 20 percent to 40 percent of people *without* narcolepsy carry these HLA types (National Institute of Neurological Disorders and Stroke [NINDS], 2009).

Hypocretin (also called orexin) is a peptide that modulates activity in the hypothalamus (the region in the brain associated with sleep, well-being, and appetite). Hypocretin specifically has properties that promote wakefulness and inhibits REM sleep. Hypocretin may also have other actions that affect feeding behavior and increase activity in the autonomic (sympathetic) nervous system and systems that regulate motor control. Deficiencies in this peptide have been observed in most patients with narcolepsy who also have cataplexy. Deficiencies might set off the following chemical responses that may produce sleep attacks:

- Low levels of histamine, a chemical that promotes wakefulness;
- Low levels of epinephrine (commonly known as adrenaline), a hormone important in alertness and arousal;
- Increase in the acetylcholine, which affects REM sleep;
- Changes in the enzyme monoamine oxidase, which is believed to be important in preventing arousal;
- Changes in dopamine, an important neurotransmitter (chemical messenger in the brain) that helps regulate sleep;
- Lower levels of leptin, a hormone associated with obesity when levels decline (people with narcolepsy tend to be overweight);
- Higher-than-normal secretion of growth-hormone during the day, which may play a role in sudden falling-asleep episodes.

Diagnostic criteria

Narcolepsy with cataplexy can be diagnosed on purely clinical grounds, but additional tests are useful to confirm the diagnosis, according to the diagnostic guidelines of the ICSD-2 (Table 3). Nocturnal polysomnography, followed by a MSLT, is recommended to assess the severity of sleepiness and diagnose other concomitant sleep disorders. For narcolepsy without cataplexy, an all-night polysomnography frequently shows a short sleep latency of less than 10 minutes and a short REM sleep latency. Stage 1 sleep and the number of wakenings may be increased. The MSLT demonstrates a mean latency of less than eight minutes, typically less than five minutes, and two or more Sleep-Onset Rapid Eye Movement Sleep Periods (SOREMPs).

Approximately 15 percent of patients with narcolepsy with cataplexy, especially patients older than 36 years of age, may have normal or borderline MSLT results. Typing for HLA almost always

shows a presence of HLA DQB1*0601 (and DR2 or DRB1*1501 in Caucasians and Asians), but this is not a diagnostic criterion for narcolepsy. Typing is most useful to exclude a diagnosis of narcolepsy with cataplexy in selected cases.

Most patients with narcolepsy without cataplexy show an MSLT with a mean latency less than or equal to eight minutes or two or more SOREMPs. Measuring cerebral spinal fluid hypocretin-1 is highly specific and sensitive for the diagnosis of narcolepsy without cataplexy. In contrast, values below 110 pg/ml (one-third of mean control values) are highly specific but are only rarely observed in cases of narcolepsy without cataplexy.

The major challenge in establishing a diagnosis of narcolepsy due to a medical condition is the determination of whether the associated medical condition or neurological disorder is causing the narcolepsy or is merely associated with the condition.

Table 3 summarizes the diagnostic criteria guidelines as they are described by the ICSD-2.

Table 3: Diagnostic Criteria for Types of Narcolepsy

Disorder/ ICD-9 Code	Diagnostic Criteria	Symptoms or features	Alternate Names
Narcolepsy With Cataplexy 347.01	• The patient has a complaint of EDS occurring almost daily for at least three months. • A definite history of cataplexy, defined as sudden and transient episodes of loss of muscle tone triggered by emotions, is present. • The diagnosis of narcolepsy with cataplexy should, whenever possible, be confirmed by nocturnal polysomnography followed by an MSLT; the mean sleep latency on MSLT is less than or equal to 8 minutes and 2 or more SOREMPs are observed following sufficient nocturnal sleep (min. 6 hours) during the night prior to the test. Alternatively, hypocretin-1 levels in the cerebrospinal fluid (CSF) are less than normal or equal to 110 pg/mL or one-third of mean normal control values. • The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.	• Sleep paralysis • Hypnagogic hallucinations • Nocturnal sleep disruption • Memory lapse • Ptosis • Blurred vision • Diplopia • Increased BMI • RBD	Gelineau Syndrome
Narcolepsy Without Cataplexy 347.00	• The patient has a complaint of EDS occurring almost daily for at least three months. • Typical cataplexy is not present, although doubtful or atypical cataplexy-like episodes may be reported. • The diagnosis of narcolepsy without cataplexy must be confirmed by nocturnal polysomnography followed an MSLT; the mean sleep latency on MSLT is less than or equal to 8 minutes, and 2 or more SOREMPs are observed following sufficient nocturnal sleep (min. 6 hours) during the night prior to the test. • The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.	• Memory lapse • Ptosis • Blurred vision • Diplopia • Nightmares • RBD • Frequent nocturnal sleep disruption • Cataplexy-like episodes	NA

Narcolepsy Due to Medical Condition (Without Cataplexy	• The patient has a complaint of EDS occurring almost daily for at least three months.
	• One or more of the following must be observed:
	  ○ Definite history of cataplexy;
	  ○ If Cataplexy is not present or is very atypical, polysomnographic monitoring performed over the patient's habitual sleep period followed by an MSLT
		• Daytime sleepiness
		• Sleep paralysis
		• Hypnagogic hallucinations
		• Insomnia
			Secondary narcolepsy, symptomatic narcolepsy

Disorder/ ICD-9 Code	Diagnostic Criteria	Symptoms or features	Alternate Names
347.10) (**With Cataplexy** 347.11)	must demonstrate a mean sleep latency on the MSLT of less than 8 minutes with 2 or more SOREMPs, despite sufficient nocturnal sleep prior to the test (minimum 6 hours). ○ Hypocretin-1 levels in the CSF are less than 110 pg/mL (or 30 percent of normal control values), provided the patient is not comatose. • A magnificent underlying medical or neurological disorder accounts for the daytime sleepiness. • The hypersomnia is not better explained by another sleep disorder, mental disorder, medication use, or substance use disorder.		

Source: AASM (2005)
BMI = Body mass index
CSF = Cerebrospinal fluid
EDS = Excessive daytime sleepiness
MSLT = Multiple Sleep Latency Test
RBD = REM Sleep Behavior Disorder
REM = Rapid eye movement
SOREMPs = Sleep-onset rapid eye movement sleep periods

Prevalence

Narcolepsy (with or without cataplexy) is estimated to affect about 20 to 60 per 100,000 Americans (0.02 to 0.06 percent), and appears throughout the world in every racial and ethnic group, affecting males and females equally (Hubin, Partinen, Kaprio, et al., 1994; Longstreth, Koepsell, Ton, et al., 2007; NINDS, 2009; Ohayon, Priest, Zulley, et al., 2002).

Prevalence rates appear to vary among countries. Compared to the U.S. population, for example, the prevalence rate is substantially lower in Israel (about one per 500,000) and considerably higher in Japan (about one per 600), although these discrepancies may be due to different diagnostic criteria and differences in study design (NINDS, 2009).

Narcolepsy with cataplexy is the most widely recognized and best characterized form of narcolepsy. Onset almost always occurs after 5 years of age, most typically between the ages of 15 and 25 years, with cataplexy occurring in 60 percent of diagnosed patients (Silber et al., 2002).

Impact of Narcolepsy

As noted above, the most common symptoms of narcolepsy include EDS (impacting 100 percent of individuals with the disorder), cataplexy (impacting approximately 60 percent of individuals with the disorder), sleep paralysis and hypnagogic hallucinations (impacting 40 percent to 80 percent of individuals with the disorder), and nocturnal sleep disruption (impacting approximately 50 percent of individuals with the disorder). Other symptoms associated with narcolepsy include reduced cognitive and psychomotor function. From the perspective of those involved in driver safety, the most worrisome symptoms associated with narcolepsy are EDS, cataplexy, and the impact of the disorder on cognitive and psychomotor function.

Cataplexy is a sudden and transient episode of loss of muscle tone, often triggered by emotions. Triggers are usually positive emotions (e.g., laughter, elation, or surprise) but are sometimes negative (e.g., anger). Cataplexy can include all skeletal muscle groups or it can be localized. The duration of cataplexy is usually short, ranging from a few seconds to several minutes at most, and recovery is immediate and complete. The loss of muscle tone experienced ranges from a mild sensation of weakness – with head drop, facial sagging, jaw weakness, slurred speech or buckling of the knees – to complete postural collapse. Twitches and jerks may occur, particularly in the face, as the patient is trying to fight the episode. The frequency for cataplexy shows wide interpersonal variation from rare events during a year-long period in some patients to countless attacks in a single day in others. Strong emotions or abrupt withdrawal from adrenergetic or serotonergic antidepressant medications may provoke successive episodes of cataplexy, termed status cataplecticus. Because this symptom results in a sudden loss of muscular control, it is of particular concern when considering the driving task.

Other symptoms of the condition include sleep paralysis, hypnagogic hallucinations and nocturnal sleep disruption, all of which may contribute to EDS associated with the disorder.

Treatment

Although there is no cure for narcolepsy, treatment options are available to help reduce the various symptoms of the disease. Treatment is generally individualized being dependent on the severity and type of the symptoms. Among the therapeutic options available are both lifestyle changes and a variety of medications. Current clinical practice guidelines from AASM and EFNS are presented in Table 4.

Medications

Several types of medications are available to individuals with narcolepsy and are prescribed based on factors such as the types of (e.g., cataplexy) and severity of symptoms experienced, other medications being taken, and response to particular drugs.

Stimulants are usually prescribed in order to treat the primary symptoms of narcolepsy (i.e., sleep attacks and EDS). Modafinil is currently the standard treatment option for these symptoms because it is not associated with the development of tolerance or the highs and lows often experienced with other stimulants. When individuals do not respond well to modafinil, they may be prescribed other stimulants including methylphenidate, and amphetamines. These may be prescribed alone or in combination with modafinil.

Several pharmacological treatment options are also available to treat symptoms of cataplexy, hypnagogic hallucinations, and sleep paralysis. Sodium oxybate is considered the standard treatment for symptoms of cataplexy and may also be effective for the treatment of hypnagogic hallucinations, sleep paralysis, and EDS. Antidepressants (e.g., tricyclics, selective serotonin reuptake inhibitors, venlafaxine, reboxetine) are also used to treat the symptoms of cataplexy, hypnagogic hallucinations, and sleep paralysis.

Lifestyle Modifications

Lifestyle modifications are usually encouraged to help increase daytime wakefulness among individuals with narcolepsy. These modifications may include having a regular nighttime sleep schedule, scheduling naps at strategic times throughout the day, regularly exercising, breaking up monotonous tasks, and avoiding nicotine and alcohol. Individuals who experience cataplexy may also be encouraged to work on avoiding situations that may trigger cataplexy and restricting emotional responses since these may bring on an episode of cataplexy.

While symptoms may be improved by adopting behavioral measures (e.g., scheduled naps), the majority of patients (94 percent) will require pharmacotherapy (Nishimo, 2007). Furthermore, behavioral interventions are generally not conducive with the unpredictable nature of the work schedule of a CMV driver. Consequently, we do not discuss behavioral interventions further in this report.

Table 4: Treatment Guidelines for Narcolepsy by AASM and EFNS

	American Academy of Sleep Medicine	European Federation of Neurological Societies
Guideline Title	**Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. 2007 Dec 1; 30(12):1705-11.**	**EFNS guidelines on management of narcolepsy. Eur J Neurol 2006 Oct; 13(10):1035-48.**
Outcomes Considered	• Reduction in daytime sleepiness • Quality of life • Adverse effects of and tolerance to medications	• Effectiveness of treatment (e.g., reduced daytime sleepiness, irresistible episodes of sleep, and cataplectic attacks; increased sleep latencies; improved sleep efficiency and overall sleep quality) • Adverse effects of medications
Major Recommendations	The following are recommended treatment options for narcolepsy • Modafinil is effective for treatment of daytime sleepiness due to narcolepsy (Standard). • Sodium oxybate is effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy. (Standard) Sodium oxybate may be effective for treatment of hypnagogic hallucinations and sleep paralysis. (Option) • Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of daytime sleepiness due to narcolepsy. (Guideline) • Selegiline may be an effective treatment for cataplexy and daytime sleepiness. (Option) • Ritanserin may be effective treatment of daytime sleepiness due to narcolepsy. (Option) • Scheduled naps can be beneficial to combat sleepiness but seldom suffice as primary therapy for narcolepsy. (Guideline) • Pemoline has rare but potentially lethal liver toxicity, is no longer available in the United States, and is no longer recommended for treatment of narcolepsy. (Option) • Tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), venlafaxine, and reboxetine may be effective treatment for cataplexy. (Guideline) • Tricyclic antidepressants, SSRIs, and venlafaxine may be effective treatment for treatment of sleep paralysis and hypnagogic hallucinations. (Option)	EDS and Irresistible Episodes of Sleep • First-line pharmacological treatment of EDS and irresistible episodes of sleep should rely on modafinil. • Second line pharmacological treatment is methylphenidate. • Of note a growing practice in the USA, based on level A evidence, of using sodium oxybate as a first line treatment of EDS. This could be the case in Europe as well, if sodium oxybate is registered for narcolepsy (including cataplexy, EDS and disturbed nocturnal sleep). In severe cases the combination of modafinil and sodium oxybate appears to be beneficial. • Behavioral treatment measures are always advisable. Essentially the studies available support on a B level the recommendation to take planned naps during the day, as naps decrease sleep tendency and shorten reaction time. Because of varying performance demands and limitations on work or home times for taking them, naps are best scheduled on a patient-by-patient basis. Cataplexy • First-line pharmacological treatment of cataplexy is sodium oxybate. • Second-line pharmacological treatments are antidepressants. Tricyclic antidepressants, particularly clomipramine, are the most potent anticataplectic drugs. However they have the drawback of anticholinergic adverse effects. • SSRIs are slightly less active but have less adverse effects. • The norepinephrine/serotonin reuptake inhibitor venlafaxine is widely used today but lacks any published clinical evidence of efficacy. • Norepinephrine reuptake inhibitors, such as reboxetine and atomoxetine, also lack published clinical evidence.

Sources: AASM (2007) and EFNS (2006)
EDS = Excessive daytime sleepiness
MSLT = Multiple Sleep Latency Test
SSRIs = Selective serotonin reuptake inhibitors

Crash Statistics, Sleep-related Crash Data, and Relevant Regulations

Highway-related Occupational Injuries and Fatalities

No single source of data exists for worker injuries and fatalities resulting from work-related roadway crashes, much less those resulting from sleep-related driving incidents while working. The Census of Fatal Occupational Injuries (CFOI), a program of the Bureau of Labor Statistics (BLS), is currently one of the most widely used sources of data on occupational fatalities in the United States. According to the latest census data from the BLS (2008), there were 5,488 fatal occupational injuries in 2007. More than 2,200 (41 percent) of these fatalities were classified as transportation incidents. One quarter (n=1,423) involved workers in transportation and material moving occupations, of which approximately half occurred as highway-related incidents.

Large Truck Crash Statistics

Although occupational data from the previous section highlights total numbers of fatalities for various occupations (such as truck drivers, bus drivers, etc.), the information masks or obscures the societal impact of these occupational fatalities (particularly those related to highway accidents) on the civilian population.

According to the National Highway Traffic Safety Administration (NHTSA), in 2007 there were:

- 37,248 fatal crashes;
- 1,711,000 injury crashes;
- 4,275,000 property damage only crashes;
- 6,024,000 total crashes.

Large trucks are associated with a significant portion of U.S. traffic crashes. Table 5 presents 2007 statistics on U.S. police-reported crashes based on NHTSA statistics from the Fatality Analysis Reporting System (FARS) and the General Estimates System (GES). Additional tables include the most recent reports on large truck crash facts for 2006, released by the Analysis Division of the FMCSA (FMCSA, 2008), and the Motor Carrier Management Information System (MCMIS). Additional but limited large truck crash data for 2007 are also described when available (FMCSA, 2009).

Table 5: 2007 Police Reported Motor-Vehicle Traffic Crashes

Crash Types	Crashes Involving Large Trucks/Buses	All Crashes	Large Truck / Buses (%)
Fatal	4,808 / 322	37,248	13% / 1%
Injury	86,245 / 16,237	1,711,000	5% / 1%

Source: FMSCA (2009)

As shown in Table 5, of the 37,248 fatal crashes occurring in 2007, 13 percent of them involved large trucks, with a total of 4,808 people killed. The majority of fatalities associated with large truck crashes occur to persons outside the truck. These are mostly occupants of other vehicles (e.g., passenger cars

and light trucks and vans), but also include nonoccupants such as pedestrians and bicyclists. Of the 4,808 fatalities and 86,245 injuries that resulted from crashes involving large trucks in 2007, approximately 17 percent of those killed and 22 percent of those injured were large-truck occupants (FMCSA, 2009). The remainder of deaths and injuries were to passenger-vehicle occupants and/or pedestrians. The total number of large truck and bus crashes has remained relatively constant over the past six years. As listed in Table 6 (also shown graphically in Sources: FARS = Fatality Analysis Reporting System, and MCMIS = Motor Carrier Management Information System

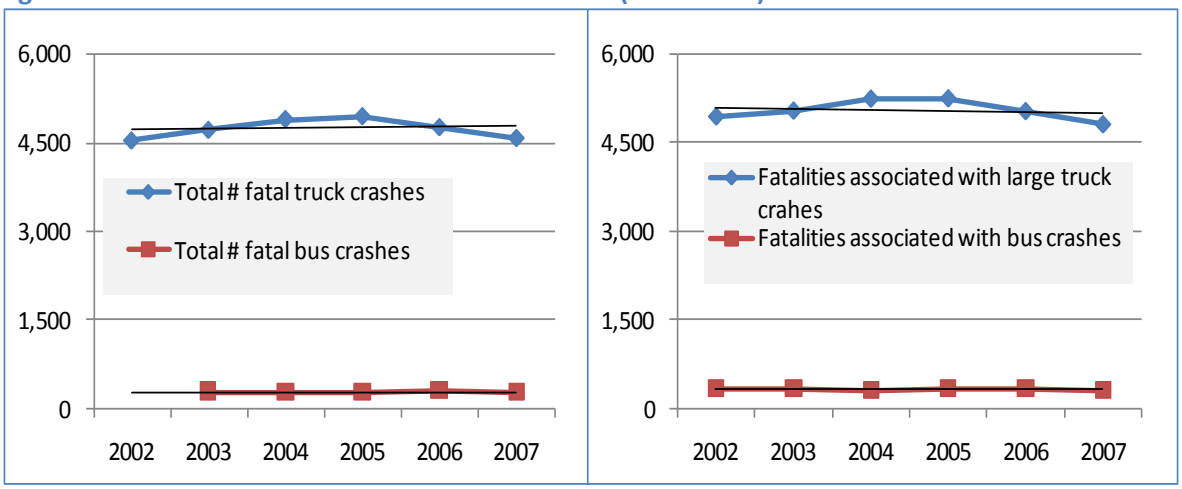
Figure 3), since 2002 there have been, on average, approximately 4,700 fatal crashes involving trucks, resulting in, on average, a little over 5,000 fatalities, annually.

Table 6: Fatal and Nonfatal Crash Rates with Large Trucks and Buses

Number of LARGE TRUCKS Involved in:	2002	2003	2004	2005	2006	2007
Fatal and Nonfatal Crashes (FARS & MCMIS)	116,651	127,948	139,321	147,154	147,091	147,533
Fatal Crashes	4,452	4,721	4,902	4,951	4,766	4,584
Nonfatal Crashes (MCMIS)	112,064	123,227	134,419	142,203	142,325	142,949
Injury Crashes (MCMIS)	55,646	58,532	60,776	61,748	60,216	58,043
Fatalities (FARS)	4,939	5,036	5,235	5,240	5,027	4,808
Injuries (MCMIS)	85,916	89,285	91,775	93,505	90,284	86,245
Number of BUSES Involved in:	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**
Fatal and Nonfatal Crashes (FARS & MCMIS)	7,039	8,555	9,172	11,146	12,507	13,506
Fatal Crashes		291	279	280	305	278
Nonfatal Crashes (MCMIS)	6,765	8,264	8,893	10,866	12,202	13,228
Injury Crashes (MCMIS)	3,944	5,033	5,218	6,140	6,905	7,130
Fatalities (FARS)	331	337	315	340	337	322
Injuries (MCMIS)	9,946	12,153	12,744	14,985	16,234	16,237

Sources: FARS = Fatality Analysis Reporting System, and MCMIS = Motor Carrier Management Information System

Figure 3: Fatal and Nonfatal Truck and Bus Crashes (2002-2006)



While the number of large trucks and buses involved in fatal crashes and fatalities have remained constant over the years, the number of fatalities per 100 million vehicle miles traveled has decreased (See Table 7 and Figure 4). In 2007, the number of large trucks in fatal crashes per 100 million vehicle miles traveled by large trucks was 2.02 – down 20 percent since 1998 when it was 2.52. Similarly, the number of large trucks involved in injury crashes per 100 million vehicle miles traveled was 33.4 – down 26 percent since 1998 when it was 45.1. Of these, large truck tractors pulling semi-trailers accounted for 62 percent of the large trucks involved in fatal crashes.

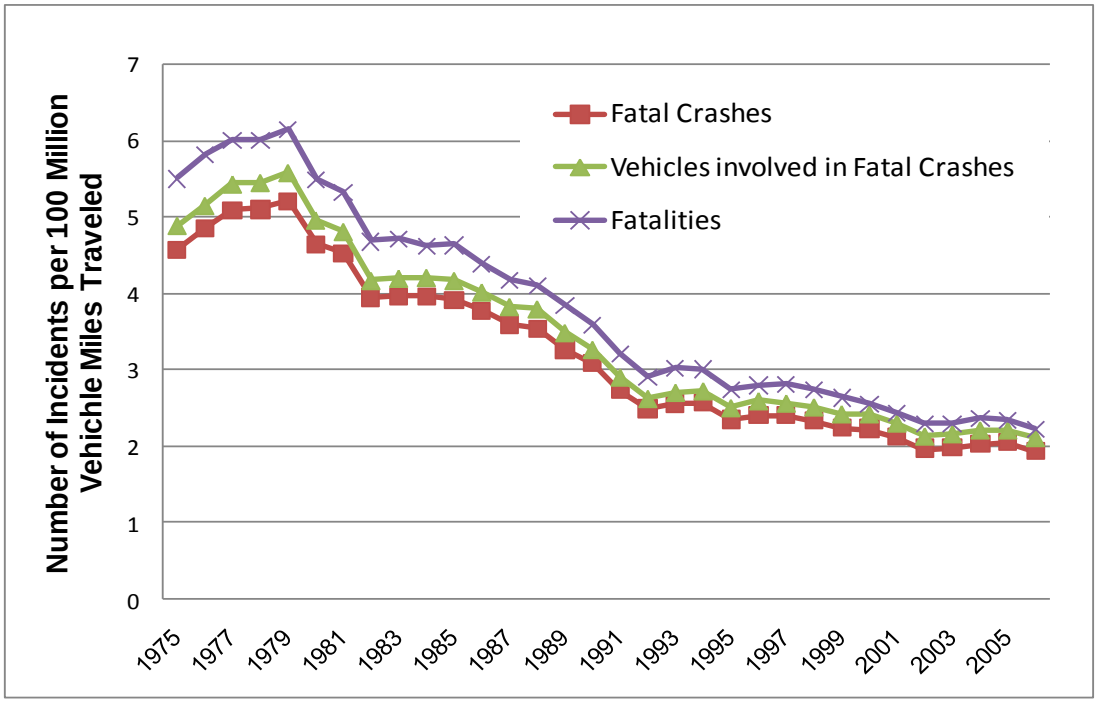
Table 7: Large Truck Crash Statistics by Exposure, 1975-2006

Year	Vehicles involved in Fatal Crashes per 100 MVMT	Fatalities per 100 MVMT	# of Large Trucks Registered
1975	4.89	5.51	5,362,369
1976	5.15	5.82	5,575,185
1977	5.43	6.02	5,689,903
1978	5.45	6.01	5,859,807
1979	5.58	6.15	5,891,571
1980	4.96	5.50	5,790,653
1981	4.81	5.34	5,716,278
1982	4.17	4.69	5,590,415
1983	4.20	4.73	5,508,392
1984	4.21	4.63	5,401,075
1985	4.17	4.64	5,996,337
1986	4.02	4.40	5,720,880
1987	3.83	4.19	5,718,266
1988	3.80	4.12	6,136,884
1989	3.49	3.85	6,226,482
1990	3.27	3.60	6,195,876
1991	2.91	3.22	6,172,146
1992	2.63	2.91	6,045,205

Year	Vehicles involved in Fatal Crashes per 100 MVMT	Fatalities per 100 MVMT	# of Large Trucks Registered
1993	2.71	3.04	6,088,155
1994	2.73	3.02	6,587,885
1995	2.51	2.76	6,719,421
1996	2.60	2.81	7,012,615
1997	2.57	2.82	7,083,326
1998	2.52	2.75	7,732,270
1999	2.43	2.65	7,791,426
2000	2.43	2.57	8,022,649
2001	2.31	2.45	7,857,675
2002	2.14	2.30	7,927,280
2003	2.17	2.31	7,756,888
2004	2.22	2.37	8,171,364
2005	2.22	2.35	8,481,999
2006	2.12	2.24	8,819,007
2007 *(Prelim)*	2.02	--	--

Source: FMSCA (2009)

Figure 4: Large Truck Crash Rates by Miles Traveled, 1975-2006



Impact of Fatigue, Sleepiness, and Sleep-related Disorders on Driving Ability

According to a report released by the NHTSA (2008, updated 2009), there were 41,059 motor-vehicle deaths (including vehicle occupants, motorcyclists, pedestrians, etc.) in 2007. Another 2.5 million individuals were injured. Based on police reports of factors involved for fatal accidents, approximately 2.5 percent involved fatigue, drowsiness, and/or falling asleep at the wheel. Similar statistics for large

truck crashes reported in 2006 (FMCSA, 2008) suggest that at least 1.5 percent of all fatal crashes involving large trucks were the result of driver fatigue, drowsiness, and/or falling asleep at the wheel.

Other reports, based on more detailed assessments of smaller, but representative, samples of truck crashes have identified fatigue and sleep-related factors at a much higher rate – up to 25 percent. For instance, the preliminary data from the Large Truck Crash Causation Study (LTCCS; Craft, 2007) suggests that driver fatigue and inattention (including that which arises from sleepiness) is a factor in as many as 13 percent and 9 percent, respectively, of large truck crashes that occurred during the period April 1, 2001, to December 31, 2003 (based on a sample of 1,000 crashes studied).

Current Relevant Medical Fitness Standards and Guidelines for CMV Drivers in the United States

Relevant Medical Fitness Standards for Medical Examiners

Under current medical qualification standards for fitness to drive a CMV [49 CFR 391.41(b)], there are no regulations that specifically address the condition of narcolepsy (either with or without cataplexy). The regulations specified in §391.41(b)(8) regarding epilepsy or any other condition that may result in loss of consciousness, and §391.41(b)(9) regarding mental, neurological, organic, or psychiatric disorders—are both somewhat relevant to the current topic as relevant conditions considered under both of these rules could include sleep disorders such as narcolepsy. These rules are given in Box 2 (see also, http://www.fmcsa.dot.gov/rules-regulations/administration/fmcsr/fmcsrruletext.asp?section=391.41). In 1988 FMCSA published the outcome of a conference organized to review the current medical standards covering neurologic disease, which included discussion of sleepiness and sleep disorders (see: http://www.fmcsa.dot.gov/facts-research/research-technology/publications/medreports.htm). This report includes recommendations to FMCSA related to sleep disorders (largely those pertaining to sleep apnea syndrome [SAS] and narcolepsy), among numerous other recommendations for other neurologically-related conditions. Recommendations specific to narcolepsy are presented in Box 2.

Box 2: Relevant FMCSA Regulations, Guidance, and Medical Expert Recommendations

Regulation
A person is physically qualified to drive a CMV if that person: **391.41 (b)(8)** Has no established medical history or clinical diagnosis of epilepsy or any other condition which is likely to cause loss of consciousness or any loss of ability to control a CMV. **391.41(b)(9)** Has no mental, nervous, organic, or functional disease or psychiatric disorder likely to interfere with the driver's ability to drive a CMV safely.
1988 Conference on Neurological Disorders and Commercial Drivers
Sleep Disorders and Interstate Driving Guidelines for Patients with Narcolepsy Syndrome: Narcolepsy is generally a lifelong condition, although the sleep attacks can be shortened or reduced in number by pharmacologic treatment in some patients. But these drugs also have other side effects, which generally do not control the sleep attacks completely. Patients with narcolepsy syndrome should not, therefore, be allowed to participate in interstate driving.

Regulatory Medical Fitness Standards and Guidelines in Other Countries

The effect of sleep disorders, sleepiness, and EDS on CMV driving is a worldwide concern. This section highlights the standards and guidelines established by other countries regarding medical fitness to drive. Regulations and guidelines from the following nations are included:

- **Australia** (Accessing Fitness to Drive; Medical Standards for Licensing and Clinical Management Guidelines; 2006)**;**
- **Canada** (Canadian Council of Motor Transport Administrators [CCMTA] Medical Standards for Drivers; 2006)**;**
- **New Zealand** (Medical Aspects of Fitness to Drive. A Guide for Medical Practitioners; Land Transport Safety Authority; 2002)**;**
- **Sweden** (Swedish National Road Administration provisions on the medical requirements for possession of a driving license, etc.; 1998);
- **United Kingdom** (For Medical Practitioners: At A Glance Guide to the Current Medical Standards of Fitness to Drive, Issued by Drivers Medical Group, Driver and Vehicle Licensing Agency of the Department for Transport (DVLA), Swansea; 2009).

Regulatory standards and guidelines pertaining to sleep-related disorders, specifically narcolepsy in CMV driving, are presented in Table 8 and Table 9.

Table 8 provides a quick-view assessment of the similarities between the regulations and guidance of other countries compared to the U.S. Table 9 provides a more detailed assessment of the regulations from other countries. The U.S. regulations are presented in Box 2, and are not reiterated in Table 9.

Table 8: Quick-view Assessment of the Attributes of Standards by Different Countries

	AUS	CAN	NZ	SWE	UK
Addresses narcolepsy specifically	•	•	•	•	•
Standard does not allow individuals with narcolepsy to drive at all		•			
Conditional licenses granted to individuals with narcolepsy	•		•	•	•
Cataplexy considered a disqualifying condition with no exception	•		•		
Exception allows use of medication to treat disorder	•		•	•	•
Advises that drivers suspected of having the disorder be tested	•		•		
Tends to grant licenses on an individual basis			•	•	•
Requires assessment or testing	•		•	•	•

Commercial driving standards from each country considered in Table 8 vary regarding narcolepsy. All but the United States address narcolepsy specifically in their driving standards. Of the five countries considered in Table 8, Australia, which allows individuals with narcolepsy to drive via a conditional license, offers the most specific criteria. This country takes a pro-stance toward narcolepsy, stating that

the disorder can be managed effectively with naps and a stimulant. However, it offers few standards regarding the use of drugs that treat the condition. Canada is the strictest country, not allowing any exception for individuals with narcolepsy to drive a CMV. New Zealand is the most lenient country in allowing individuals with narcolepsy to drive with the exception of those who have severe symptoms. However, these individuals must be tested and gain the approval of a doctor, whose diagnosis likely will rely on a patient questionnaire. Each person is to be considered separately, according to New Zealand's additional guidelines. Sweden does not allow an individual with narcolepsy to drive a CMV unless they are treated successfully. The country fails to define what successful means. The United Kingdom generally will deny a CMV license for individuals with narcolepsy, but will consider granting them to those who have had their disease under control for an undefined period of time.

Table 9: Sleep Disorders and Driving – Guidelines and Standards from Other Countries

Country	**Australia,** *Accessing Fitness to Drive; Austroads Inc. 2003 (reprinted 2006)*
Source	**http://www.austroads.com.au/cms/AFTD%20web%20Aug%202006.pdf**

Standard	**Medical Standards for Licensing – Sleep Disorders**
	The criteria for an unconditional license are **NOT** met:
	• If narcolepsy is confirmed.
	A ***conditional license*** may be granted by the Driver Licensing Authority, taking into account the opinion of a specialist in sleep disorders, and the nature of the driving task, and **subject to periodic (at least annual) review**, after the following requirements are met:
	• A clinical assessment has been made by a sleep physician;
	• Cataplexy has not been a feature in the past;
	• Medication is taken regularly;
	  • There has been an absence of symptoms for **6 months;**
	  • Normal sleep latency present on MWT (on or off medication). (Expert Opinion).

Additional Guidance	**20.1 RELEVANCE TO DRIVING TASK** **20.1.5** Those with narcolepsy perform worse on simulated driving tasks and are more likely to have vehicle crashes than control subjects. **20.2 GENERAL MANAGEMENT GUIDELINES** 20.2.2 Increased sleepiness during the daytime in otherwise normal people may be due to prior sleep deprivation (restricting the time for sleep), poor sleep hygiene habits, irregular sleep wake schedules or influence of sedative medications including alcohol. Insufficient sleep (less than five hours) prior to driving is strongly related to motor vehicle crash risk. EDS may also result from a number of medical sleep disorders including the sleep apnea syndromes (obstructive sleep apnea, central sleep apnea and nocturnal hypoventilation), periodic limb movement disorder, circadian rhythm disturbances (e.g. advanced or delayed sleep phase syndrome), some forms of insomnia and narcolepsy. **20.2.5 Narcolepsy** Narcolepsy is present in 0.05% of the population and usually starts in the second or third decade of life. Sufferers present with excessive sleepiness and can have periods of sleep with little or no warning of sleep onset. Other symptoms include cataplexy, sleep paralysis and vivid hypnagogic hallucinations. The majority of sufferers are HLA-DR2 positive. There is a sub-group of individuals who are excessively sleepy, but do not have all the diagnostic features of narcolepsy. Inadequate warning of incoming sleep, and cataplexy, put drivers at high risk. Diagnosis of narcolepsy is made on the combination of clinical features, HLA typing and MSLT with a diagnostic sleep study on the prior night to exclude other sleep disorders and aid interpretation of the MSLT. Subjects suspected of having narcolepsy should be referred to a sleep physician or neurologist for assessment (including a MSLT) and management. They should have a review at least annually by their specialist. Sleepiness in narcolepsy can usually be managed effectively with scheduled naps and stimulant medication. Tricyclic antidepressants and MAO inhibitors are used to treat cataplexy.
Country	**Canada,** *CCMTA MEDICAL STANDARDS FOR DRIVERS (revised Jul 2006)*
Source	**http://www.ccmta.ca/english/pdf/medical_standards_july06.PDF**
Standard	**6.4 Narcolepsy and Other Sleep Disorders** Individual is not eligible to operate a Class 1, 2, 3 or 4 motor vehicle (commercial vehicles).

Additional Guidance	**6.4.1 Narcolepsy** Patients who suffer attacks of narcolepsy should generally not be allowed to drive any type of motor vehicle. If they respond favorably to treatment and are experiencing no side effects from medication, they may drive Class 5 or 6 vehicles after 3 months. However, they should not be allowed to hold a Class 1, 2, 3 or 4 license.
	• **Class 1**: Permits the operation of a motor vehicle of any type or size, with or without passengers, and a trailer of any size. • **Class 2**: Permits the operation of a motor vehicle of any type or size, with or without passengers. A Class 2 license does not permit the holder to pull a semi-trailer. • **Class 3:** Permits the operation of a motor vehicle of any size. A Class 3 license does not permit the holder to carry passengers or to pull a semi-trailer. • **Class 4:** Permits the operation of a taxicab, a bus carrying no more than 24 passengers and emergency response vehicles, such as ambulances, fire trucks and police cars. • **Class 5**: Permits the operation of any motor vehicle or small truck (a towed vehicle cannot exceed 4600 kg). A Class 5 license does not permit the holder to drive an ambulance, a taxicab or a bus or to pull a semi-trailer. • **Class 6**: Permits the operation of a motorcycle, motor scooter or mini-bike only. All other classes must be endorsed to include Class 6 before the holder may operate a motorcycle, motor scooter or mini-bike.
Country	**New Zealand,** *Medical aspects of fitness to drive. A guide for Medical Practitioners, Land Transport Safety Authority (2002)*
Source	**http://www.landtransport.govt.nz/licensing/docs/ltsa-medical-aspects.pdf**
Standard	**10.1.2 Narcolepsy** Individuals who have severe narcolepsy or narcolepsy with excessive sleepiness or cataplexy are generally considered unfit to drive a commercial vehicle. **When driving may occur or may resume** Individuals may resume driving or can drive if their condition is adequately treated under specialist supervision with satisfactory control of symptoms. Consideration should be given to the type of driving and hours of driving an individual undertakes. If there is any residual risk of daytime sleepiness medical practitioners should recommend a restriction in working hours or shift work. The Director of Land Transport Safety or the Director's delegate may impose license conditions for regular medical assessment. Medical follow-up may be delegated to the General Practitioner.
Additional Guidance	**10.1 EDS** Sleepiness can be classified as follows: ***mild sleepiness*** — describes infrequent sleeping during times of rest or when little attention is required ***Moderate sleepiness*** — describes sleep episodes that occur on a regular basis during activities requiring some degree of attention. Examples of such include attending conferences, movies or the theatre, group meetings, operating machinery or watching children ***Severe sleepiness*** — describes sleep episodes that are present daily and during activities that require sustained attention. Examples include eating, direct personal conversation, walking and physical activities, as well as operating motor vehicles. The most common cause of excessive sleepiness is insufficient sleep. Shift-work, time of day (circadian factors), sedatives, and alcohol may increase sleepiness. Two conditions are of importance in respect of daytime drowsiness, i.e. obstructive sleep apnea and narcolepsy. Both conditions have been associated with significantly higher rates of crashes, and those people suffering from these conditions tend to underestimate their level of daytime sleepiness (Parkes, 1983 and Straddling 1989). Whenever these conditions are suspected in any individual, they should be fully investigated by the appropriate specialists and treatment instituted. It is important to appreciate that the degree of impairment of driving skills varies widely between obstructive sleep apnea (OSA) sufferers, reflecting individuals' differing ability to cope with sleep disruption (George et al, 1996) and the severity of the OSA. Similar comments apply to narcolepsy. This makes blanket advice to all patients with OSA very difficult. The situation is further compounded by a lack of a validated objective measure of sleepiness and difficulty gaining access to sleep investigations in some parts of New Zealand. Repeated testing to monitor improvement following therapy is not a realistic option. Thus medical practitioners should be aware that assessment of sleepiness is principally by individuals' own subjective assessment using questionnaires; the validity of questionnaire assessment on a given individual cannot be assured. Those with severe disease, as documented by a sleep study, or a previous sleep-related motor vehicle accident, appear to be in the high risk category. Medical practitioner assessment is required to evaluate the cause of symptoms, assess the severity of sleepiness, provide initial treatment recommendations and, where appropriate, refer an individual for specialist evaluation. **10.1.2 Narcolepsy** This condition is often associated with cataplexy. Features such as transient diplopia, automatic behavior and memory lapses have also been reported in some cases. The condition is usually life-long and will require continuing medication. Not all individuals with narcolepsy suffer the full range of symptoms and not all suffer from unpredictable episodes of cataplexy. Consideration of the individual's circumstances should be undertaken.

Country	Sweden *(1998)*
Source	www.transportstyrelsen.se/Global/Publikationer/Vag/VVFS/9889eng000915.pdf?epslanguage=sv
	Chapter 11 Alertness Disorders ***Possession*** 1. OSA, rhonchopathy ("snoring disease"), narcolepsy or other diseases characterized by alertness disorders that imply a danger to traffic safety constitute grounds for denial of possession. This, however, does not apply in the case of successful treatment. 2. Regarding possession in Groups II and III, due consideration shall be given to the additional risks and dangers to traffic safety involved in such possession. **Reappraisal** 3. A reappraisal shall occur at intervals considered suitable in each individual case.
Country	**United Kingdom** *(2009)*
Source	http://www.dvla.gov.uk/medical/ataglance.aspx
	Chapter 1: Neurological disorders Narcolepsy GROUP 2 ENTITLEMENT VOC – LGV/PCV Generally considered unfit permanently, but if a long period of control has been established licensing may be considered on an individual basis.

EDS = Excessive daytime sleepiness
HLA-DR2 = Broad antigen serotype associated with narcolepsy
MAO = Monoamine oxidase inhibitor (type of antidepressant)
MSLT = Multiple Sleep Latency Test
MWT = Maintenance of Wakefulness Test
OSA = Obstructive sleep apnea

Medical Fitness Standards and Guidelines for Individuals Performing Transportation Safety in the United States

Current relevant medical fitness standards and guidelines for individuals performing transportation safety in the United States are summarized in Table 10. Included in the table are pertinent rules and guidance for pilots, railroad workers, and merchant mariners.

Medical fitness-for-duty programs in the transportation industry vary greatly. A pilot's medical fitness is determined by the FAA, which has specific standards (14 CFR 67) and detailed guidance for first-, second-, and third-class airmen. Class 1 medical certificates are required for commercial pilots or airline transport pilots. This class of individuals has the most stringent medical requirements. Class 2 medical certificates are for commercial, non-airline duties such as crop dusters, charter pilots, and corporate pilots. Class 3 medical certificates are for private pilot activities only. The latter class of individuals has the least restrictive medical requirements. According to FAA regulations only a limited number of trained and designated aviation medical examiners (AMEs) are able to perform these examinations. As shown in Table 10, while the FAA does not present a rule specific to narcolepsy, it does specify that an individual having a history of disturbance of consciousness would not meet criteria for a medical license.

Railroad fitness for duty regulations are covered by the FRA medical standards. In contrast to other modes of transportation, FRA medical standards are limited in scope (covering only vision and hearing, 49 CFR 240.121). The railroads are responsible for ensuring that the engineer meets the medical standards. The U.S. Coast Guard (USCG) and MARAD also provide fitness for duty standards and guidance. There are three categories of mariner rating: licensed, qualified, and unqualified or entry level

ratings. Licensed includes officers, masters, and mates. This category has the strictest set of licensing requirements. Sailors are in the qualified category and have requirements that are similar to those for a licensed position. The entry level rating is for an individual with no mariner skills. These regulations address vision and hearing requirements (46 CFR 10, 12, and 13). More extensive general health requirements are detailed in associated medical guidance (revised most recently in September 2008). According to these guidelines, individuals with narcolepsy (among other sleep disorders) require individualized review.

Table 10: Standards and Guidelines for Sleep Disorders from other U.S. Government Transportation Safety Agencies

Condition	FAA* (all classes of airmen)	Railroad†	Merchant Mariner‡
Sleep Disorder and/or other Relevant Condition	§ 67.109, 67.209, & 67.309 Neurologic. Neurologic standards for a first-, second-, and third-class airman medical certificate are: (a) No established medical history or clinical diagnosis of any of the following: • Epilepsy; • A disturbance of consciousness without satisfactory medical explanation of the cause; or • A transient loss of control of nervous system function(s) without satisfactory medical explanation of the cause. (b) No other seizure disorder, disturbance of consciousness, or neurologic condition that the Federal Air Surgeon, based on the case history and appropriate, qualified medical judgment relating to the condition involved, finds: • Makes the person unable to safely perform the duties or exercise the privileges of the airman certificate applied for or held; or • May reasonably be expected, for the maximum duration of the airman medical certificate applied for or held, to make the person unable to perform those duties or exercise those privileges.	No specific standards or guidelines	46: Shipping MERCHANT MARINER CREDENTIAL § 10.215 Medical and physical requirements. (d) General medical exam. (1) This exam must be documented and of such scope to ensure that there are no conditions that pose an inordinate risk of sudden incapacitation or debilitating complication. This exam must also document any condition requiring medication that impairs judgment or reaction time. Examples of physical impairment or medical conditions that could lead to disqualification include, but are not limited to, poorly controlled diabetes, myocardial infarctions, psychiatric disorders, and convulsive disorders. MEDICAL AND PHYSICAL EVALUATION GUIDELINES FOR MERCHANT MARINER CREDENTIALS Sleep Apnea, Central Sleep Apnea, Narcolepsy, Periodic Limb Movement, Restless Leg Syndrome or other sleep disorders. *Recommended Evaluation Data* Submit all pertinent medical information and status report. Include sleep study with a polysomnogram, use of medications and titration study results. If surgically treated, should have post operative polysomnogram to document cure or need for further treatment.

*Source of information for FAA Regulations and Guidelines:
http://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/media/guide.pdf

† Source of information for Federal Railroad Administration Guidelines:
http://www.fra.dot.gov/downloads/safety/hazmatch4.pdf

‡ Source of information for Merchant Mariner Guidelines:
http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=98052981cf71e9e8e2b1416486073f1d&rgn=div5&view=text&node=46:1.0.1.2.10&idno=46#46:1.0.1.2.10.2.7.9
http://www.uscg.mil/hq/cg5/NVIC/pdf/2008/NVIC_4-08.pdf

Methods

This section provides a synopsis of how we identified and analyzed information for subsequent sections of this evidence report. This section briefly covers the questions addressed in each of these sections, the literature searches performed, the primary qualifications for inclusion of the literature that was examined, and the statistical techniques that were utilized to synthesize data across studies. Specific details of study quality assessment, statistical approaches used, etc., are documented in appendices.

Key Questions

FMCSA was interested in examining several issues pertaining to the potential impact of narcolepsy on CMV driver safety.

In the early scope development work conducted by the Agency and the MRB, the following issues of concern were raised:

1. Does narcolepsy result in an increased risk of CMV crash? Does narcolepsy result in an increased risk of personal vehicle crash?
2. Is there experimental evidence that narcolepsy results in driving impairment (e.g., driving simulator studies)?
3. Is there quality evidence that treatment of narcolepsy reduces risk of crash to that of the appropriately certified commercial vehicle driving population? Is there quality evidence that treatment of narcolepsy reduces risk of personal vehicle crashes to that of the healthy general driving population?
4. Does use of modafinil to treat narcolepsy reduce risk of CMV crash to that of the appropriately certified commercial vehicle driving population? Does use of modafinil for treatment of narcolepsy reduce risk of personal vehicle crash to that of the healthy general driving population?

As indicated above, these issues revolved around the impact of the disorder itself on the driving task. Specifically, the Agency was interested in determining the magnitude of the risk for crash that is associated with the disorder, the factors associated with the disorder that potentially increase this crash risk, and the impact of current treatment options on crash risk.

Symptoms of narcolepsy that are known to be associated with reduced driving performance and increased crash risk have been discussed in Section 1 of this report. Specifically these symptoms include the following:

- EDS
- Reductions in cognitive and psychomotor function
- Sudden incapacitation consequent to cataplexy

The remaining two issues of interest to the Agency – crash risk associated with narcolepsy and the impact of treatment on this crash risk.

The specific key questions of the Agency and the MRB described above were reframed for the purpose of the evidence report, as follows:

Key Question 1: Are individuals with narcolepsy (with or without cataplexy) at an increased risk for a motor vehicle crash when compared to comparable individuals without the disorder?

Outcomes to be assessed are the following:

- Crash risk (CMV and private license holders)
- Driving performance (simulated or observed)

Key Question 2: Do currently recommended treatments for narcolepsy reduce the risk for a motor vehicle crash?

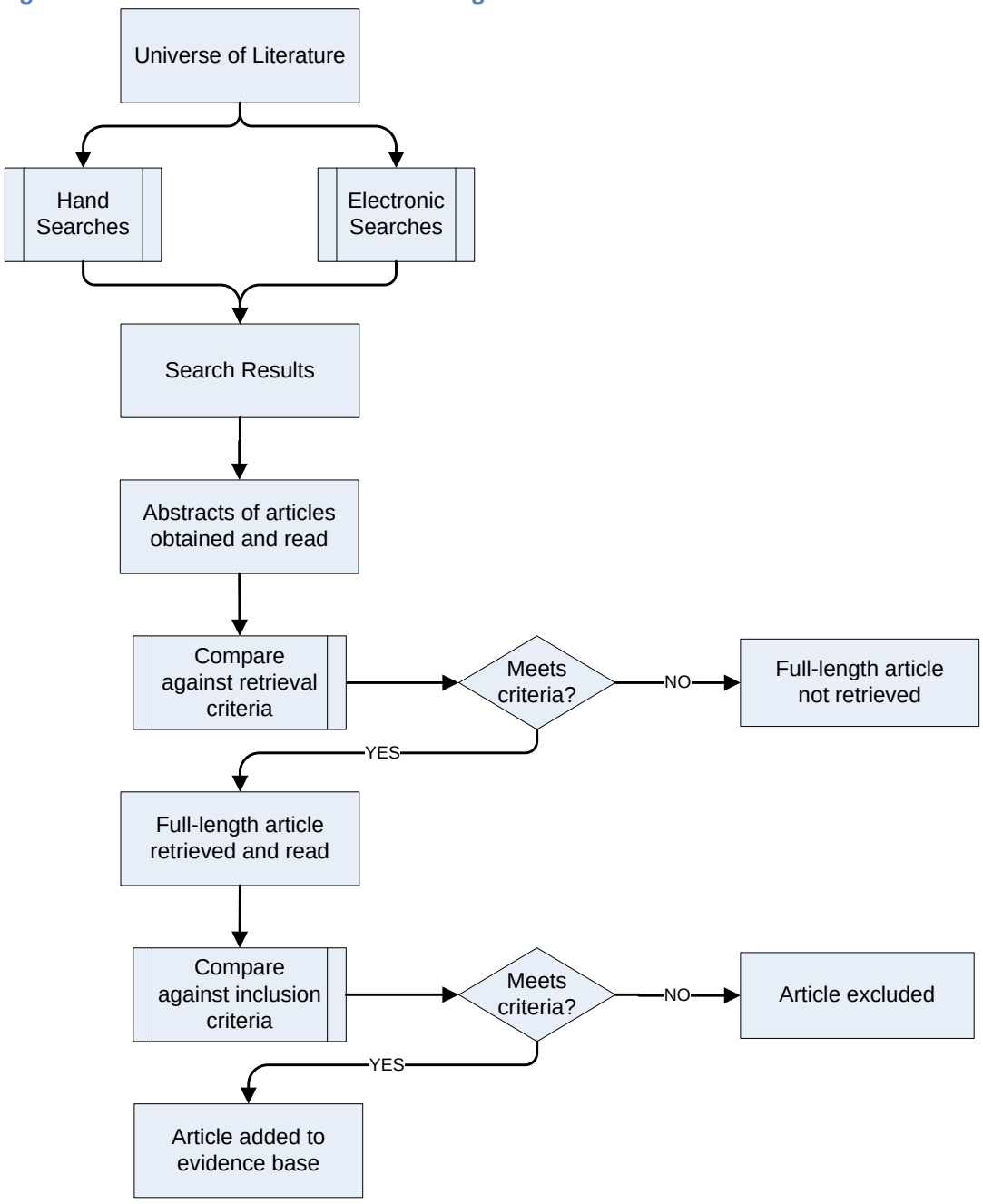
Outcomes to be assessed are the following:

- Crash risk (CMV and private license holders)
- Simulated driving performance
- Cataplexy
- Measures of cognitive and psychomotor function

Identification of Evidence Bases

The evidence bases used in this evidence report were identified using the multistage process captured by the algorithm presented in Figure 5. The first stage of this process consists of a comprehensive search of the literature. 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 5: 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 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.

Electronic Searches

Electronic searches of PubMed and the TRIS databases were conducted (through July 2009). Searches were conducted using a combination of free-text terms and controlled vocabulary concepts derived from the National Library of Medicine's (NLM's) Medical Subject Headings (MeSH). The primary search terms applied are listed in Table 11. Free-text terms included those related to commercial driving, traffic accidents and crash, as well as terms related to sleep disorders, sleepiness, EDS, and fatigue. Additional filter options and "related" search features, available through PubMed, were applied in subsequent searches to identify relevant literature. Filters applied to the searches included limiting the searches to English language, human studies, relevant to adults (19+ years).

Table 11: Search Terms used in Electronic Searches

Driving-Related Terms			
MeSH	Accidents, traffic Motor vehicles, buses, trucks Automobiles, automobile driving Transportation Accidents, occupational	**Free-text**	Accident, crash, collision Commercial driver, commercial truck driver, commercial motor vehicle, CMV, professional driver, lorry driver, long haul driver, CMV driver or operator
Sleep-Related Terms			
MeSH	Dysomnias, environmental sleep disorder, sleep disorders, extrinsic Sleep disorders Narcolepsy-Cataplexy Syndrome Narcoleptic Syndrome Paroxysmal Sleep	**Free-text**	Narcolepsy Narcolepsy with Cataplexy Gelineau syndrome EDS, daytime sleepiness, sleepiness, hypnolepsy, sleeping disease, and paroxysmal sleep

Manual Searches

Manual searches of relevant literature also were performed. This included the review of reference lists of retrieved articles, as well as searches of "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. Articles and technical reports reporting primary and/or secondary data were obtained and assessed for relevance to the current topic.

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. The retrieval criteria are presented in Appendix C.

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 a MANILA analyst who determined whether the 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 an article 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 reason(s) for its exclusion, are presented in Appendix D.

Evaluation of Quality and Strength 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 that was used to draw an evidence-based conclusion (Treadwell et al., 2006). Using this approach, which is described briefly in Appendix E, we took into account not only the quality of the individual studies that comprise the evidence base for each key question, but also 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 with narcolepsy are at increased risk for a motor vehicle crash") and a quantitative conclusion (e.g., "when compared to individuals who did not have a narcolepsy, the relative risk for a motor vehicle crash is 6.02; 95 percent CI 3.02 to 9.04"). As shown in Table 12, we assign 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 12: 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.
Minimally acceptable	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.
Insufficient	Although some evidence exists, the evidence is insufficient to warrant drawing an evidence-based conclusion.
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 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.
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.
Unstable	Estimates of the treatment effect are too unstable to allow a quantitative conclusion to be drawn at this time.

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 deemed to be stable are more unlikely to change significantly with the publication of new data than are unstable effect size estimates.

Statistical Methods

The set of analytic techniques used in this report was extensive. In summary, fixed- effects meta-analyses were used to pool data from different studies when heterogeneity was not present. Important differences in the findings of different studies (heterogeneity) were identified using the Q-statistic and I^2 (Gavaghan et al., 2000; Greenhouse et al., 1994; Higgins et al., 2003; Higgins et al., 2002; Petitti, 2001; Sulton et al., 2001; Takkouche et al., 1999). Whenever appropriate, heterogeneity was explored using meta-regression techniques (Higgin & Thompson, 2004; van Houwelinger et al., 2002; & Thompson & Higgins, 2002). When heterogeneity could not be explained, data from different studies were pooled using random-effects meta-analysis (Fleiss, 1994; Hedges, 1994; Hedges & Vevea, 1998; Littenberg & Moses, 1993; Mitchell, 1998; Moses & Shapiro, 1993; Parmar et al., 1998; Raudenbush, 1994; Shadish & Haddock, 1994; & Sutton et al., 2001). Sensitivity analyses, aimed at testing the robustness of our findings, were performed using cumulative random-effects meta-analyses (Conti, 1993; Duval & Tweedie, 1998 & 2000; Ioannidis et al., 1999 & 2001; Lau et al., 1995; Mottola, 1992; Olkin, 1999; Sterne, 1998; Sutton et al., 2000). All meta-analyses in this Evidence Report were performed using Comprehensive Meta-Analysis software.

We calculated three different estimates of effect in this evidence report. Between-group differences in outcome measured using continuous data were analyzed in their original metric (if all included studies reported on the same outcome using the same metric) or the data were standardized into a common metric known as the standardized mean difference (SMD). Dichotomous data were analyzed using the rate ratio (RR) or the odds ratio (OR). The formulae for these effect sizes and their variance are presented in Table 13.

Table 13: Effect Size Estimates Used in Evidence Report and their Variance

Effect size	Formula (Effect size)	Formula (Variance)
SMD	$\frac{\mu_{TG}-\mu_{CG}}{\left(\sqrt{\frac{(n_{TG}-1)(s_{TG})^2+(n_{CG}-1)(s_{CG})^2}{n_{TG}+n_{CG}-2}}\right)}$	$\frac{n_{TG}+n_{CG}}{n_{TG}n_{CG}}+\frac{SMD^2}{2(n_{TG}+n_{CG})}$
Where: μ_{TG} **= mean (treatment group);** μ_{CG} **= mean (control group);** S_{TG} **= standard deviation (treatment group);** S_{CG} **= standard deviation (control group);** n_{TG} **= enrollees (treatment group);** n_{CG} **= enrollees (control group)**		
OR	$\left(\frac{a}{b}\right)\Big/\left(\frac{c}{d}\right)=\left(\frac{ad}{bc}\right)$	$\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}$

Effect size	Formula (Effect size)	Formula (Variance)
RR	$\left(\frac{a}{a+c}\right) \Big/ \left(\frac{b}{b+d}\right)$	$\frac{1}{a}+\frac{1}{a+c}+\frac{1}{b}+\frac{1}{b+d}$
Where: a = number of individuals with disorder who crashed; b = number of individuals without disorder who crashed; c = number of individuals with disorder who did not crash; d = number of individuals without disorder who did not crash.		

OR = Odds ratio
RR = Rate ratio
SMD = Standardized mean difference

Evidence Synthesis

This section summarizes the findings of our systematic review of the evidence pertaining to each of the key questions asked by the FMCSA.

Key Question 1: Are individuals with narcolepsy (with or without cataplexy) at an increased risk for a motor vehicle crash when compared to comparable individuals without the disorder?

Introduction

As noted in Section 1 of this evidence report, narcolepsy is characterized by recurrent episodes of EDS, associated deficits in cognitive and psychomotor function and, in some individuals, temporary muscular paralysis (cataplexy), hypnagogic hallucinations, and sleep paralysis. These characteristics – specifically the occurrence of EDS, cognitive and psychomotor deficits, and cataplexy (in some individuals) – potentially result in individuals with the disorder having an increased risk for a motor vehicle crash. Given this, FMCSA was interested in determining whether there is evidence to support the supposition that individuals with a diagnosis of narcolepsy are at an increased risk for a crash. In addition, should an increased crash risk be demonstrated, the Agency was interested in determining the magnitude of this increased risk.

Identification of Evidence Base

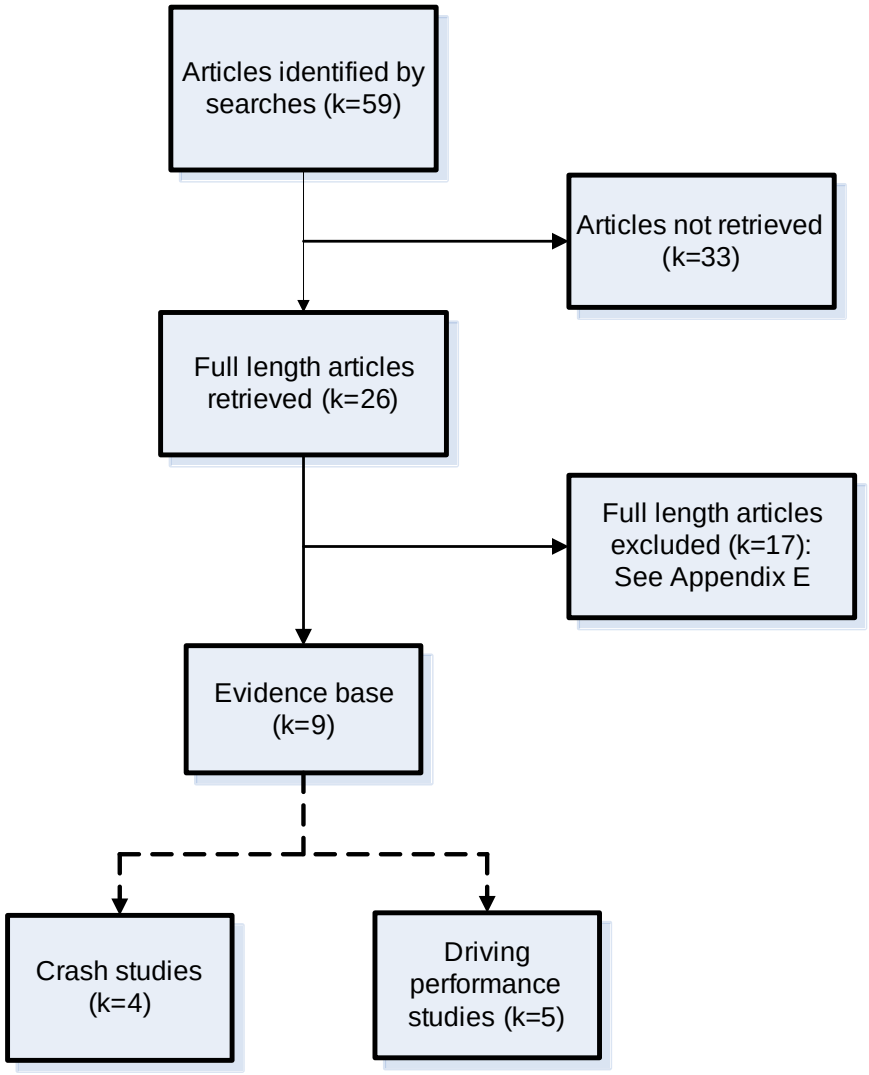
In addressing the needs of FMCSA, we were primarily interested in identifying and summarizing the findings of studies that attempted to directly determine the risk for a motor vehicle crash associated with narcolepsy. Studies of secondary interest to us were studies that attempted to evaluate the relationship between narcolepsy and indirect measures of driver safety such as measures of driving performance (as measured by naturalistic studies, closed course driving studies, or driving simulator studies).

The evidence base identification pathway for this section of the evidence report is summarized in Figure 6. Our searches identified a total of 59 articles that were potentially relevant to this key question. Following application of the retrieval criteria for this question (see Appendix C for description of retrieval criteria), 26 full-length articles were retrieved and read in full. Nine of these retrieved articles were found to meet the inclusion criteria for this key question (see Appendix D for description of inclusion criteria).

Of the nine studies identified by our searches, four provided direct evidence pertaining to the impact of narcolepsy on driver safety *(Aldrich, 1989; Broughton et al., 1981; Broughton, Guberman, & Roberts, 1984; Ozaki et al., 2008).* The remaining five studies examined the impact of narcolepsy on driving performance *(Findley et al., 1995; Findley, Suratt, & Dinges, 1999; George, Boudreau, & Smiley, 1996; Kotterba et al., 2004; Mitler, Hajdukovic, & Erman, 1993)*. All five of the latter studies examined driving

performance using a simulator. No naturalistic driving studies or closed course driving performance studies were identified.

Figure 6: Evidence Base Identification Pathway for Key Question 1



Evidence Base

This subsection provides a brief description of the key attributes of the nine studies that compose the evidence base for Key Question 1. Here we discuss applicable information relevant to the quality of the included studies and the generalizability of each study's findings to CMV drivers.

Characteristics of Included Studies

As noted above, four crash studies and five driving performance studies met the inclusion criteria for this section of the evidence report. These studies along with a summary of their primary design characteristics are presented in Table 14.

Studies Providing Direct Evidence - Crash Studies

All four crash studies used a retrospective cohort design, in which the crash history of cases was compared to the crash history of controls. These studies provided crash data from which crash risk could be determined in drivers with narcolepsy. In three of these studies, individuals with narcolepsy (cases) were compared to individuals without narcolepsy (controls) (Aldrich, 1989; Broughton et al., 1981; Broughton et al., 1984). In the fourth study, the two groups being compared consisted of individuals with narcolepsy and cataplexy and individuals with narcolepsy and no cataplexy (Ozaki et al., 2008). The purpose of the former three studies was to determine if individuals with narcolepsy are at a higher risk for a crash than individuals who do not have the disorder. The purpose of the latter study was to determine whether individuals with a diagnosis of narcolepsy with cataplexy are at higher risk for a crash than individuals with narcolepsy without cataplexy.

Consistent with the aims of the included studies, the primary outcome of interest was the occurrence of a motor vehicle accident due to sleepiness. However, Ozaki and colleagues (2008) used a composite measure consisting of crashes and "near-misses" as their primary outcome measure. In addition to crash data, three of the four included studies (Aldrich, 1989; Broughton et al., 1981; Broughton et al., 1984) also presented data pertaining to a number of surrogate outcomes for crash (e.g., incidences of near misses, incidence of sleeping while driving, incidence of occurrence of cataplexy/sleep paralysis while driving). In all four crash studies, outcomes were self-reported by subjects.

Studies Providing Indirect Evidence - Driving Performance Studies

Five included studies examined various measures of driving performance as assessed using computerized driving simulator programs (Findley et al., 1995; Findley et al., 1999; George et al., 1996; Kotterba et al., 2004; Mitler et al., 1993). These studies all used a prospective cohort study design, in which cohorts of individuals with or without a diagnosis of narcolepsy engaged in a test of simulated driving performance (e.g., driving simulation) and the results were then compared.

The primary outcome of interest in four out of the five simulator studies was the number of obstacles hit on a driving simulator test (Findley et al., 1995; Findley et al., 1999; Kotterba et al., 2004; Mitler et al., 1993). Kotterba and colleagues (2004) also examined the mean number of concentration lapses (e.g., using headlights) during the simulator test. These studies used either the Steer Clear Driving Simulator (Findley et al., 1995; Findley et al., 1999; Mitler et al., 1993) or the Computer Aided Risk Simulator (Kotterba et al., 2004). George, Boudreau, and Smiley (1996) used the Divided Attention Driving Test in their study to examine the primary outcomes of tracking error (i.e., lane position variability) and response to visual targets.

Table 14: Key Characteristics of Studies: Narcolepsy, Crash Risk and Driving Performance

Reference	Year	Design	Comparison	n=	Diagnosis Criteria	Primary Outcome(s)	Outcome Self-reported?	Medication being used to treat narcolepsy?	Driving Exposure Controlled for?
Crash Studies: Narcolepsy vs. No Narcolepsy									
Aldrich	1989	Retrospective Cohort	Individuals without a history of sleep disorders Matched for age and sex	Comparison: 70 Narcolepsy: 56	NR	Crash Near accidents	Yes	No	No
Broughton et al.	1981	Retrospective Cohort	Individuals without a history of narcolepsy Matched for age and sex	Comparison: 180 Narcolepsy: 180	NR	Crash Near accidents Falling asleep during driving Cataplexy while driving Sleep paralysis while driving	Yes	Yes	No
Broughton, Guberman, & Roberts	1984	Retrospective Cohort	Individuals without a history of sleep disorders	Comparison: 60 Narcolepsy: 60	NR	Crash Near accidents Falling asleep during driving	Yes	Yes	No
Crash Studies: Narcolepsy with Cataplexy vs. Narcolepsy without Cataplexy									
Ozaki et al.	2008	Retrospective Cohort	Comparisons made between groups diagnosed with narcolepsy with cataplexy and narcolepsy without cataplexy	Narcolepsy with Cataplexy: 28 Narcolepsy without Cataplexy: 27	ICSD-2 criteria; MSLT ≥ 2 sleep-onset REM periods and < 8 min mean sleep latency	Crash or near crash	Yes	No	No

Reference	Year	Design	Comparison	n=	Diagnosis Criteria	Primary Outcome(s)	Outcome Self-reported?	Medication being used to treat narcolepsy?	Driving Exposure Controlled for?
Driving Performance Studies									
Findley et al.	1995	Prospective Cohort	Individuals without a history of daytime sleepiness Matched for age and sex	Comparison: 10 Narcolepsy: 10	Symptoms (sleep attacks, cataplexy, and/or sleep paralysis); five-nap MSLT: mean sleep latency < 10 minutes and ≥ 1 sleep-onset REM periods	Obstacles hit on driving simulation test (i.e., vigilance)	No	No	NA
Findley, Suratt, & Dinges	1999	Prospective Cohort	Individuals without a history of narcolepsy or obstructive sleep apnea	Comparison: 14 Narcolepsy: 16	Symptoms (sleep attacks, cataplexy, and/or sleep paralysis); five-nap MSLT: mean sleep latency < 10 minutes and ≥ 1 sleep-onset REM periods	Obstacles hit on driving simulation test (i.e., vigilance)	No	No	NA
George, Boudreau, & Smiley	1996	Prospective Cohort	Individuals without a history of daytime sleepiness	Comparison: 21 Narcolepsy: 16	NR	Tracking error Response to visual targets	No	No	NA
Kotterba et al.	2004	Prospective Cohort	Individuals without diseases of the central nervous system, snoring, daytime sleepiness, or any use of medication	Comparison: 10 Narcolepsy: 13	Symptoms (EDS, cataplexy, and sleep paralysis); MSLT ≥ 2 sleep-onset REM periods; HLA DR15/DQ*0602 positivism	Obstacles hit on driving simulation test Concentration lapses on driving simulation test	No	Yes (5 patients on medication)	NA
Mitler, Hajdukovic, & Erman	1993	Four-Condition Double-Blind, Randomized Crossover*	Individuals with no history of narcolepsy Matched for age, sex, education, and work	Comparison: 8 Narcolepsy: 8	Symptoms (excessive somnolence, hypnagogic hallucinations and/or cataplexy);	Obstacles hit on driving simulation test	No	No	NA

Reference	Year	Design	Comparison	n=	Diagnosis Criteria	Primary Outcome(s)	Outcome Self-reported?	Medication being used to treat narcolepsy?	Driving Exposure Controlled for?
					four nap MSLT mean sleep latency < 5 minutes and ≥ 2 SOREMPs				

*Only baseline data for each group was used in Key Question 1 analyses
EDS = Excessive daytime sleepiness
ICSD-2 = International Classification of Sleep Disorders
MSLT = Multiple Sleep Latency Test
NA = Not applicable
NR = Not reported
REM = Rapid eye movement
SOREMPs = Sleep onset REM periods

Quality of Evidence Base

The Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies was used to examine the quality of all the included studies. A complete description of this instrument and detailed results of our quality assessments are presented in Appendix F and Appendix G respectively. The findings of our assessment of the quality of each of the nine studies included in the evidence base for this section of the evidence report are summarized in Table 15.

Table 15: Quality of the Studies: Narcolepsy, Crash risk and Driving Performance

Reference	Year	Quality Scale Used	Quality Rating
Crash Studies			
Aldrich	1989	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Low
Broughton et al.	1981	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Low
Broughton, Guberman, & Roberts	1984	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Low
Ozaki et al.	2008	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Low
Driving Performance Studies			
Findley et al.	1995	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Findley, Suratt, & Dinges	1999	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
George, Boudreau, & Smiley	1996	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Kotterba et al.	2004	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Mitler, Hajdukovic, & Erman	1993	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate

All four crash studies received a “Low” quality rating whereas the five driving performance studies were rated “Moderate”. Although observational studies often statistically adjust for known confounding factors, only random allocation can control for unknown confounding. Therefore, the quality rating of cohort studies can never be “High”. The main reasons for the “Low” rating of the crash studies were the use of self-reported outcome data and lack of control for differences in driving exposure. Differences in driving exposure (e.g., number of miles driven per unit of time) are of particular importance to studies that examine motor vehicle crash risk. No data on driving exposure was collected in these studies therefore it is possible that drivers with narcolepsy drove much less than individuals without narcolepsy, which could lead to an underestimation of crash risk compared with controls. Self-reported data can also introduce bias to a study and affect the validity of the findings. The two types of bias that are particularly troublesome with self-reported data are response bias and recall bias. Response bias occurs when subjects distort their responses to present themselves in a particular way and recall bias occurs when subjects have difficulty remembering that a particular event occurred in the past.

Generalizability of Evidence to Target Population

The purpose of this section is two-fold. First, the section examines the degree to which individuals with narcolepsy included in the evidence base are generalizable to individuals with narcolepsy in the general population. Second, the section provides details of the extent to which individuals enrolled in the studies that are assessed in this section of the evidence report are similar to CMV drivers in the United States. Determining the generalizability of the individuals enrolled in the included studies to the general

population of individuals with narcolepsy and to CMV drivers requires an examination of two important sources of information: the inclusion and exclusion criteria of each included study and an examination of the demographic characteristics of the enrollees.

The inclusion and exclusion criteria for each of the studies assessed in this section of the evidence report are presented in Table 16.

Table 16: Study Inclusion and Exclusion Criteria: Narcolepsy, Crash risk and Driving Performance

Reference	Year	Inclusion Criteria	Exclusion Criteria	Other Relevant Characteristics
Crash Studies				
Aldrich	1989	Cases: Narcolepsy diagnosis based on clinical evaluation and sleep study results Controls: No diagnosis of a sleep disorder based on clinical evaluation and sleep study results	Cases & Controls: Not current driver; taking stimulant medication at time of the sleep study	Cases: Recruited from a sleep disorders center over a 3-year period Controls: Mainly medical center employees or spouses of patients with sleep disorders
Broughton et al.	1981	Cases: Narcolepsy diagnosis based on having either daytime sleepiness or actual sleep attacks plus one or more REM based auxiliary symptoms (i.e., cataplexy, sleep paralysis, hypnagogic hallucinations) Controls: Not considered to have narcolepsy	Cases & Controls: Not current driver*	Cases: Recruited from three sleep centers in North America, Asia, and Europe Controls: Some controls reported difficulty with sleeping such as restless night sleep, excessive drowsiness, vivid imagery on falling asleep, and sleep paralysis
Broughton, Guberman, & Roberts	1984	Cases: History of irresistible sleep attacks and cataplexy with or without sleep paralysis or vivid hypnagogic hallucinations Controls: Normal subjects not taking CNS active medication	Cases & Controls: Not current driver*	Cases: NR Controls: Largely hospital employees and colleagues
Ozaki et al.	2008	Cases & Controls: ≥ 20 years; narcolepsy diagnosis based on criteria of ICSD-2 and sleep study results Cases: History of cataplexy Controls: No history of cataplexy	Cases & Controls: Co-morbid sleep disorders; psychiatric disorders; other major medical illnesses; medication use; not current driver*	Cases & Controls: Recruited from the outpatient clinic of the Japan Somnology Center
Driving Performance Studies				
Findley et al.	1995	Cases: Narcolepsy diagnosis based on clinical evaluation and sleep study results; currently untreated Controls: No symptoms of EDS	Cases: NR Controls: NR	Cases: NR Controls: Employees at the University of Virginia
Findley, Suratt, & Dinges	1999	Cases: Narcolepsy diagnosis based on polysomnography; currently untreated Controls: No history of sleep apnea or narcolepsy; no symptoms of sleep disturbance or EDS	Cases: NR Controls: NR	Cases: NR Controls: Employees at the University of Virginia
George, Boudreau, & Smiley	1996	Cases: Diagnosis based on clinical examination Controls: No complaints of sleepiness; no current use of CNS active drugs	Cases & Controls: Not current or past driver; physical disability; current use of hypnotics/sedatives or stimulants; hypothyroidism	Cases: Recruited from the Victoria Hospital Sleep Disorders Clinic Controls: Recruited from the community
Kotterba et al.	2004	Cases: Narcolepsy diagnosis based	Cases & Controls: History of head	Cases: NR

Reference	Year	Inclusion Criteria	Exclusion Criteria	Other Relevant Characteristics
		on symptoms, sleep study results, and HLA testing; driving license ≥ 2 years; drive car ≥ 4 days a wk Controls: Healthy; no diseases of the central nervous system; no history of cerebral neurological disorder, snoring, daytime sleepiness, or current medication use; driving license ≥ 2 years; drive car ≥ 4 days a wk	injury, cerebral ischemia; encephalitis; alcohol or drug abuse	Controls: NR
Mitler, Hajdukovic, & Erman	1993	Cases: clinical history of excessive somnolence; mean sleep latency on four-nap MSLT of < 5 minutes; history of hypnagogic hallucinations and/or cataplexy; no other sleep pathology; ≥ 2 transitions to REM sleep on MSLT; willingness to take a stimulant drug Controls: Healthy; no sleep disorders based on polysomnography	Cases: NR Controls: NR	Cases: Recruited from sleep disorders clinic Controls: Recruited from bulletin board notices and word of mouth

*Individuals who were not current drivers were excluded from analyses on driving outcomes
EDS = Excessive daytime sleepiness
HLA DR 15/DQ*0602 = Antigens/genetics associated to narcolepsy
ICSD-2 = International Classification of Sleep Disorders
MSLT = Multiple Sleep Latency Test
NR = Not reported
REM = Rapid eye movement

In most included studies, narcolepsy subjects were recruited from sleep disorder clinics and therefore, are representative of the narcolepsy population currently receiving treatment. While this most likely captures the majority of individuals with narcolepsy, it may not represent more mild cases (i.e., individuals who do not need routine treatment). Diagnoses of narcolepsy, in these studies, were primarily based on medical standards (e.g., medical history, clinical presentation, sleep study results).

Many studies excluded subjects (both cases and controls) if they were currently taking medication, however, in three studies, this was not an excludable criterion (Broughton et al., 1981; Broughton et al., 1984; Kotterba et al., 2004). This criterion creates two different populations of individuals. Those who are not currently taken medication represent the “untreated” population and examining driving outcomes in this population allows one to control for the possible effects of medication on driving. The other group of individuals (i.e., those currently take medication) better represents the “treated” population.

All of the crash studies and three of the driving performance studies specifically stated that they excluded individuals if they were not current drivers. This is an important criterion because if studies did include individuals with little or no driving experience, one might expect to see poorer results than are presently observed because of the additional crash risk associated with a lack of experience. Also, these studies may not represent the entire narcolepsy population in that they probably excluded more severe cases of narcolepsy because these individuals would be more likely to choose not to drive. None of the crash studies controlled for driving exposure (i.e., distance driven over a specific period of time) among

their subjects. This is an important point given that differences in crash rates can often be explained by differences in the amount of time spent driving.

Other important characteristics of the individuals enrolled in the studies assessed in this section of the evidence report are presented in Table 17. The generalizability of the findings of the included studies to CMV drivers is unclear as none of the included studies examined narcolepsy specifically among CMV drivers. The mean age of participants included in these studies (range: 31.2 years to 55.1 years) is relatively comparable to the average age of CMV drivers (43 years), however, females were largely over-represented in these studies compared to the CMV driver population. Also, driving exposure was not reported in any of the included studies, so consequently, comparability to CMV drivers could not be assessed. This is important to note given that CMV drivers generally have greater risk exposure because they spend more time driving than non-CMV drivers.

Table 17: Characteristics of Enrolled Individuals: Narcolepsy, Crash Risk and Driving Performance Studies

Reference	Year	Number of Individuals with Narcolepsy Included (n=)	Age Distribution	% Male	% CMV Drivers	Driving Exposure (e.g., average miles driven annually)	Race/Ethnicity (%)	Generalizability to CMV Drivers
Crash Studies								
Aldrich	1989	56	Cases: 44.8* Control: 44.5	Cases: 69 Controls: 50	NR	NR	NR	Unclear
Broughton et al.	1981	180	Cases: 41.9 ± 11.3 Controls: 41.9 ± 11.4	Cases: 62 Controls: 62	NR	NR	Canadian: 33 Japanese: 33 Czech: 33	Unclear
Broughton, Guberman, & Roberts	1984	60	Cases: 41.4 ± 11.1 Controls: 32.0 ± 8.4	Cases: 45 Controls: 45	NR	NR	Canadian: 100	Unclear
Ozaki et al.	2008	55	31.2 ± 9.2	48	NR	NR	Japanese: 100	Unclear
Driving Performance Studies								
Findley et al.	1995	10	Cases: 37 ± 5 Controls: 35 ± 1	Cases: 30 Controls: 30	NR	NR	NR	Unclear
Findley, Suratt, & Dinges	1999	16	Cases: 38 ± 19 Controls: 43 ± 15	Cases: 56 Controls: 79	NR	NR	NR	Unclear
George, Boudreau, & Smiley	1996	16	Cases: 39.6 ± 15.2 Controls: 46.1 ± 15.1	Cases: 75 Controls: 100	NR	NR	Canadian: 100	Unclear
Kotterba et al.	2004	13	Cases: 40.9 ± 12.4 Controls: 55.1 ± 7.8	Cases: 77 Controls: 90	NR	NR	NR	Unclear
Mitler, Hajdukovic, & Erman	1993	8	Cases: 42.0* Controls: 43.1	Cases: 38 Controls: 38	NR	NR	NR	Unclear

*Standard deviation not reported
NR = Not reported

Findings

Direct Evidence – Narcolepsy and Crash

Individuals with Narcolepsy vs. Individuals without Narcolepsy

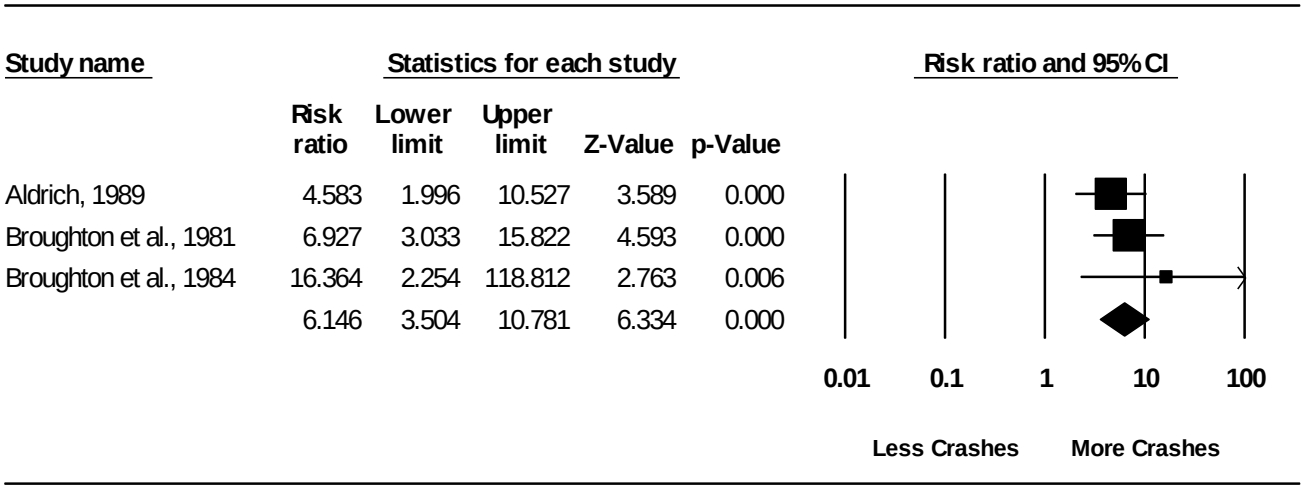
Table 18 presents the findings from the three studies that reported on the incidence of crashes occurring among individuals with narcolepsy and the incidence of crashes occurring among individuals without narcolepsy (Aldrich, 1989; Broughton et al., 1981; Broughton et al., 1984).

Table 18: Crash Risk in Drivers with Narcolepsy Compared to Drivers without Narcolepsy

Reference	Year	Units	Crash Rate Data					Evidence of increased crash risk?
			Cases	Controls	Risk Ratio (95% CI)	Controlled for…	*P* =	
Aldrich	1989	Crashes per driver	0.39	0.086	4.58 (1.74, 12.07)	Age and sex	0.001	Yes
Broughton et al.	1981	Crashes per driver	0.37	0.053	6.98 (2.77, 17.31)	Age, sex, driving status	0.00002	Yes
Broughton, Guberman, & Roberts	1984	Crashes per driver	0.34	0.021	16.2 (2.07, 129.06)	Sex, driving status	0.004	Yes

These three studies (Quality Rating: "Low") provided adequate data to determine an estimate of a crash risk and 95 percent confidence intervals (CI) between individuals who have narcolepsy and comparable individuals who do not have narcolepsy. None of the three studies, however, reported the time period over which crashes were examined, therefore, our calculations reflect risk ratios rather than risk rate ratios. Homogeneity testing found these studies to be homogeneous (Q=1.496, p=0.473, I^2=0); therefore, these data were pooled using a fixed effects meta-analysis (Figure 7).

Figure 7: Crash Risk among Individuals with Narcolepsy Compared to Controls (Fixed Effects Meta-Analysis)



The findings of this meta-analysis provide support for the contention that individuals with narcolepsy are at a significantly increased risk for experiencing a motor vehicle crash when compared to comparable individuals without narcolepsy (summary crash rate ratio = 6.15, 95% CI: 3.51, 10.8; p = 0.000). In other words, these findings indicate that individuals with narcolepsy are approximately six times more likely to experience a crash compared to individuals without narcolepsy. Sensitivity analyses found these findings to be robust (Appendix H). While the quality of the studies was not high, the data were consistent and the magnitude of the difference in crash risk is very large. Consequently, one can be reasonably confident that future research findings are unlikely to overturn these findings.

Narcolepsy with Cataplexy vs. Narcolepsy without Cataplexy

One of the included studies (Quality Rating: "Low") compared crash rates of patients with narcolepsy with cataplexy to crash rates of patients with narcolepsy without cataplexy (Ozaki et al., 2008). Crash rate data from this study is presented in Table 19.

Table 19: Crash Rate Data for Individuals with Narcolepsy with Cataplexy vs. Narcolepsy without Cataplexy

Reference	Year	Units	Crash Rate Data					Evidence of increased crash risk?
			Cases*	Controls	Rate Ratio (95% CI)	Controlled for…	*P* =	
Ozaki et al.	2008	Crashes or near crashes in past 5 years per driver	0.75	0.50	1.5 (0.46, 4.86)	Driving status	0.25	No

*Cases: Narcolepsy with cataplexy; Controls: Narcolepsy without cataplexy

These results of the study did not show a significant difference in crash rates among individuals with narcolepsy with cataplexy and those without cataplexy. As previously mentioned, however, in this study, the rates of actual crashes and near-miss crashes were combined in one variable. Therefore, the lack of difference found between these two groups may be due to the inclusion of near-miss crashes in this measurement. In other words, the inclusion of near-miss crashes may have diluted any differences between these two groups in rates of actual crashes. More research is needed before any conclusions can be made about the role that cataplexy may play in crash risk among individuals with narcolepsy.

Indirect Evidence – Simulated Driving Performance

Five studies (Quality Rating: "Moderate") provided simulated driving performance data (Findley et al., 1995; Findley et al., 1999; George et al., 1996; Kotterba et al., 2004; Mitler, et al., 1993). The primary outcome of interest in four of these studies was the ratio of the number of simulator crashes observed in two cohorts of individuals; those with a diagnosis of narcolepsy and healthy controls. Table 20 presents the mean percent (or number) of obstacles hit on driving simulator for each group along with the calculated standardized mean difference.

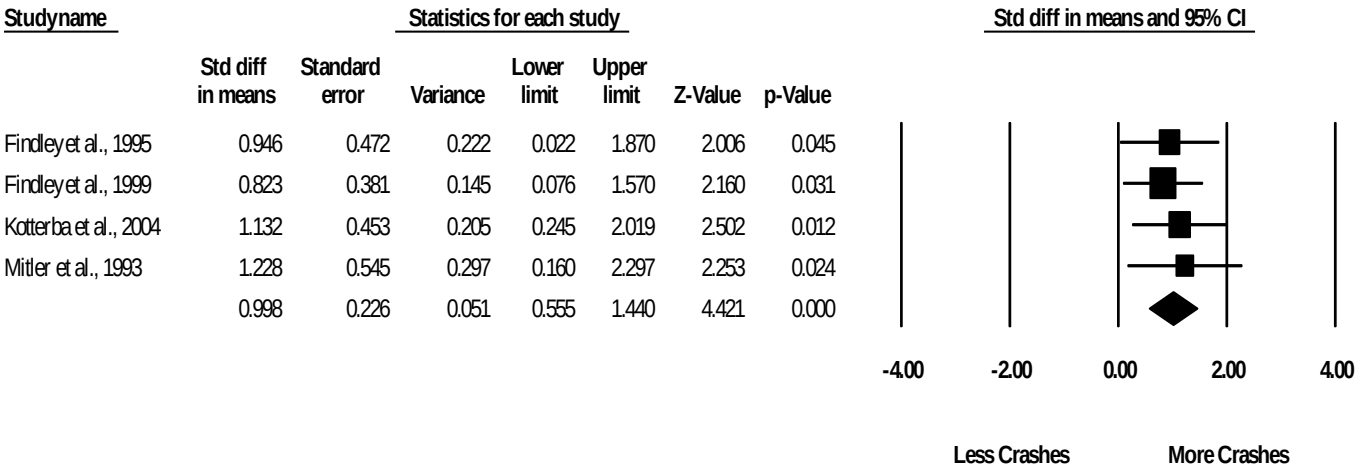
Table 20: Simulator Crash Rate Data among Drivers with Narcolepsy Compared to Drivers without Narcolepsy

Reference	Year	Units	Simulator Crash Rate Data					Evidence of Increased Risk?
			Cases	Controls	SMD (95% CI)	Controlled for…	*P* =	
Findley et al.	1995	Average percent of obstacles hit on driving simulator	7.7± 10.1	0.9 ± 0.95	0.95 (0.02, 1.87)	Age and sex	0.045	Yes
Findley, Suratt, & Dinges	1999	Average percent of obstacles hit on driving simulator	6.9± 9.6	1.1 ±0.75	0.82 (0.08, 1.57)	----------	0.031	Yes
Kotterba et al.	2004	Average number of obstacles hit on driving simulator	3.2± 1.8	1.3 ± 1.5	1.13 (0.25, 2.02)	----------	0.012	Yes
Mitler, Hajdukovic, & Erman	1993	Average percent of obstacles hit on driving simulator	2.96± 2.23	0.83 ±1.02	1.23 (0.16, 2.30)	Age, sex, education, work history	0.024	Yes

SMD = Standardized mean difference

The effect size estimates were then pooled using meta-analysis. A test of homogeneity found that the findings of these studies were homogeneous (Q = 0.489, $p = 0.921$, $I^2 = 0$). Consequently, we pooled the data using a fixed-effects meta-analysis (Figure 8). Pooling of the data using a fixed-effects meta-analysis provided support for the contention that individuals with narcolepsy have higher rates of driving simulator crashes compared to individuals without narcolepsy (standardized mean difference (SMD) = 0.998; 95% CI: 0.56, 1.44; $p = 0.000$). According to proposed estimates as to what constitutes a small (0.3), medium (0.5), and large effect size (0.8), a summary SMD of 0.998 indicates a large effect (Cohen, 1988). Sensitivity analyses showed that these findings were robust (Appendix H).

Figure 8: Simulator Crash Risk among Individuals with Narcolepsy Compared to Controls (Fixed Effects Meta-Analysis)



George, Boudreau, and Smiley (1996) conducted a study assessing performance on a divided attention driving test in a simulated environment among individuals with and without narcolepsy. They examined a number of driving performance indicators including tracking error, number of correct responses,

response time, and number of out of bounds. Driving performance data and calculated weighted mean differences are presented in Table 21. In this study, individuals with narcolepsy had worse tracking error, fewer correct responses, and more instances of going out of bounds compared to healthy controls. No significant difference was found between the two groups on mean response time.

Table 21: Driving Performance Data among Drivers with Narcolepsy Compared to Drivers without Narcolepsy

Reference	Year	Units	Driving Performance Data					Evidence of Increased Risk?
			Cases	Controls	WMD (95% CI)	Controlled for…	*P* =	
George, Boudreau, & Smiley	1996	Mean tracking error (lane position variability)	196 ± 146	71 ± 32	125.0 (60.9, 189.1)	Driving experience	0.000	Yes
		Mean number of correct responses	35.3 ±6.2	38.4 ± 2.5	-3.1 (-6.01, -0.19)		0.04	Yes
		Mean response time (seconds)	2.9 ± 0.8	3.3 ± 1.1	-0.4 (-1.04, 0.24)		0.22	No
		Mean number of out of bounds	12.1 ± 26.8	0.1 ± 0.3	12.0 (0.59, 23.41)		0.04	Yes
Kotterba et al.	2004	Mean number of concentration lapses	9.5 ± 3.5	7.1 ±3.2	2.4 (-0.38, 5.18)	----------	0.28	No

WMD = Weighted mean difference

Kotterba and colleagues (2004) compared the number of concentration lapses (e.g., using headlights) that occurred among individuals with and without narcolepsy when tested with a computerized driving simulator (Table 21). No significance difference was found between these two groups on the number concentration lapses (9.5 ± 3.5 versus 7.1 ± 3.2, *P* = 0.28).

Summary of Findings

Currently available evidence supports the contention that drivers with narcolepsy are at an increased risk for a motor vehicle crash when compared to otherwise comparable individuals without the disorder (Strength of Evidence: Strong).

- **The estimated magnitude of increased risk is RR = 6.15 (95% CI: 3.50, 10.78) (Stability of Evidence: Moderate).**

Direct Evidence – Crash Studies: Current direct evidence from three crash studies (Quality Rating: "Low") conducted with non-CMV drivers showed that individuals with narcolepsy are at an increased risk for a crash compared to individuals who do not have narcolepsy. Pooling of these data revealed that the estimated risk of crash associated with narcolepsy is RR = 6.15 (95% CI: 3.50, 10.78), representing a six-fold increase compared to individuals without narcolepsy. Sensitivity analyses showed that these findings were robust. The data were qualitatively consistent and the effect size was large, making it unlikely that future studies will overturn this finding.

An additional study (Quality Rating: "Low") examined the effects of cataplexy on the risk of crash among individuals with narcolepsy. This study did not find a significant difference in crash risk between these two groups; however, their measure of crash was combined with a measure of near-miss crashes, so therefore, differences in the rates of actual crash may be diluted. Further studies are needed before a conclusion can be made as to the role of cataplexy in crash risk among individuals with narcolepsy.

Indirect Evidence – Risk Factor and Driving Performance Studies: Five studies (Quality Rating: "Moderate") examined factors associated with simulated driving outcomes. Four of these studies examined rates of obstacles hit during a driving simulation test. These studies provided enough data to calculate effect size estimates and conduct a meta-analysis. Pooling of these data revealed that individuals with narcolepsy have higher rates of driving simulator crashes compared to individuals without narcolepsy (standardized mean difference = 0.998; 95% CI: 0.56, 1.44; p= 0.000). A standardized mean difference of 0.998 indicates a large effect size. Sensitivity analyses found that these findings were robust.

Two studies examined other measures of simulated driving performance, namely tracking error, number of correct responses, response time, number of out of bounds and number of concentration lapses. Findings indicated that individuals with narcolepsy had significantly more tracking error, fewer correct responses, and more instances of going out of bounds compared to healthy controls. No significant differences were found between the groups for mean response time or number of concentration lapses.

In summary, while there are limitations in the designs of the studies that examined direct crash risk in this evidence base, all study results showed a strong effect size and statistical significance. Further, indirect evidence of crash is also reported and provides strong support for the direct crash study findings. Based upon available information, there is strong evidence that non-commercial drivers with narcolepsy are at an increased risk of crash.

Key Question 2: Do currently recommended treatments for narcolepsy reduce the risk for a motor vehicle crash?

Introduction

Having established that individuals with narcolepsy are at an increased risk for a motor vehicle crash we next address the issue of whether individuals who receive treatment for the disorder can be considered safe to drive. It is possible that currently available treatments for the disorder are so effective that they reduce the risk for crash to levels that are comparable to individuals who do not have the disorder.

As noted in Section 1 of this evidence report, recommended treatment options for individuals with narcolepsy include the use of amphetamines, modafinil (or armodafinil), sodium oxybate, and antidepressants. According to clinical practice guidelines from the AASM (Morgenthaler et al., 2007) and the EFNS (Billiard et al., 2006), the first-line of treatment for EDS and irresistible episodes of sleep associated with narcolepsy is modafinil. The FDA approved dose for modafinil is 200 mg given once daily in the morning. However, current guidelines recommend 100 to 600 mg/day given in two doses; one dose in the morning and one dose early in the afternoon. The second line pharmacological treatment

recommended by both groups is methylphenidate at a daily dosage of 10–60 mg. AASM also recommends amphetamine, methamphetamine, or dextroamphetamine as alternative second line treatments. For cataplexy associated with narcolepsy, both groups recommend sodium oxybate at a starting dose of 4.5 g/night divided into two equal doses of 2.25 g/night as the first line of treatment. However, in the U.S., sodium oxybate is also considered a first line treatment for EDS and disrupted sleep due to narcolepsy, as well as for the treatment of hypnagogic hallucinations and sleep paralysis. In severe cases of narcolepsy with cataplexy, a combination of modafinil and sodium oxybate has also been recommended as a first line treatment. A number of other compounds are used to a limited degree when other treatments have failed. For instance, tricyclic antidepressants (such as clomipramine), SSRIs (fluvoxamine and femoxetine), SNRIs (such as venlafaxine, and reboxetine) are used for the treatment of cataplexy, sleep paralysis and hypnagogic hallucinations. Similarly, selegiline (a MAO-B inhibitor) and ritanserin (a serotonin antagonist) have been used for the treatment of EDS; however this is typically reserved for when first line treatments are unsuccessful.

In this section we examine the efficacy of current medications in the treatment of narcolepsy (with and without cataplexy), and whether or not available treatments positively affect measures of driving performance. Each of the currently recommended treatment options are addressed as subquestions of Key Question 2. Specifically, they are:

Key Question 2A: What is the impact of treatment with modafinil or armodafinil for narcolepsy on driver safety?

Key Question 2B: What is the impact of treatment with sodium oxybate for narcolepsy on driver safety?

Key Question 2C: What is the impact of treatment with antidepressants for narcolepsy on driver safety?

Key Question 2D: What is the impact of treatment with amphetamine, methylphenidate, and other stimulants for narcolepsy on driver safety?

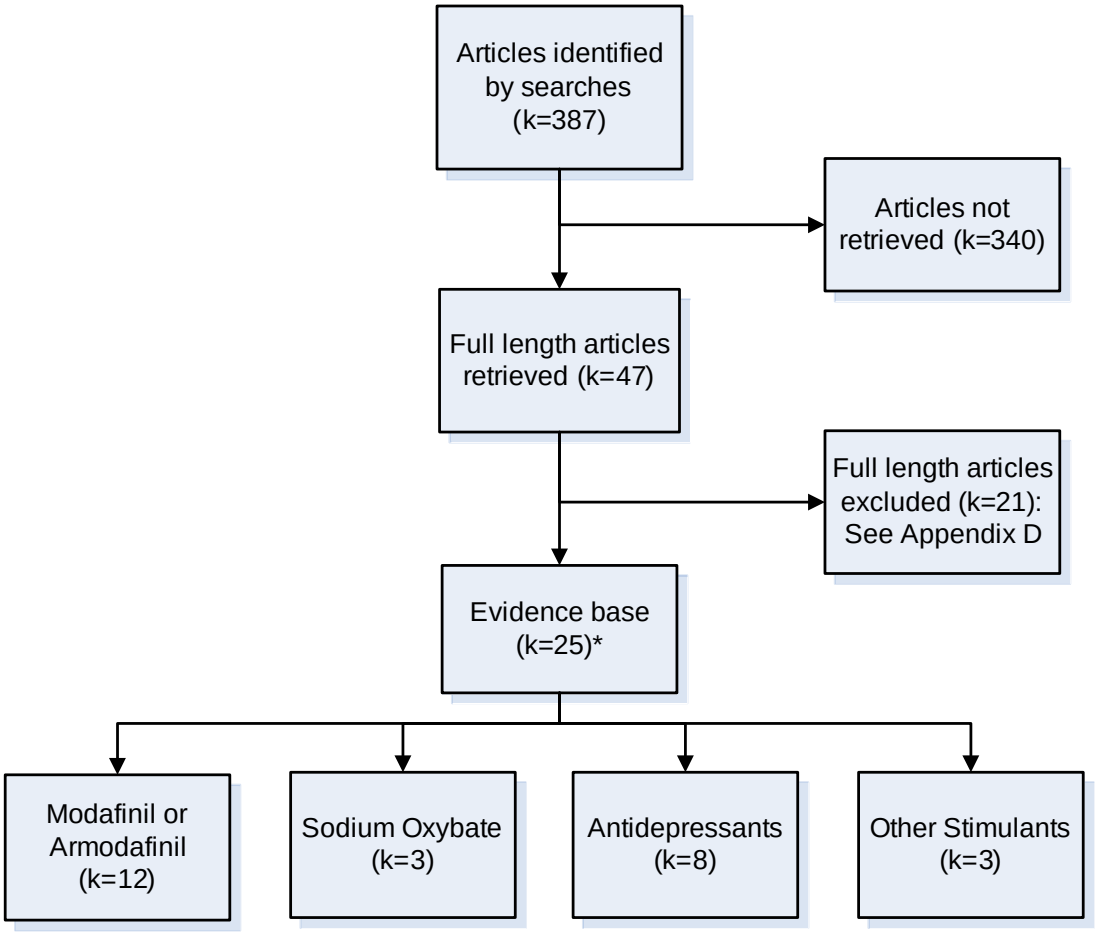
Because clinical trials of treatment efficacy are unlikely to focus on crash rates or driver performance, we determined *a priori* to expand the list of outcomes of interest to include several other outcomes. These outcomes included measures of EDS, cataplexy event rate, and measures of cognitive and psychomotor function. All three of these outcomes may be considered as surrogate markers of driving performance and crash risk. The presence of EDS and reduced cognitive and/or psychomotor function are both known to be associated with reduced driving performance and an increased risk for a motor vehicle crash. The occurrence of cataplexy while driving is an incapacitating event which is obviously detrimental to driving performance and is a clear risk factor for a motor vehicle crash.

Identification of Evidence Base

The identification of the evidence base utilized in this section of the evidence report is summarized in Figure 9. Our searches identified a total of 387 articles that appeared relevant to this key question. On comparing the abstracts for these articles against the retrieval criteria for this section listed in Appendix C, 47 full-length articles were retrieved. Twenty five of these retrieved articles were found to meet the

inclusion criteria for this section (see Appendix D for inclusion criteria). Table E- 2 of Appendix E lists the 21 articles that were retrieved but then excluded, along with a brief description of the reasons for their exclusion.

Figure 9: Evidence Base Identification Pathway – Impact of Treatment on Driver Safety



*One included study examined the efficacy and safety of two drugs considered in this evidence report; modafinil and sodium oxybate. As a consequence, the total number of studies – when considered by drug type – appears to be 26.

Table 22 identifies the 25 independent studies that were included in this section, along with the study design and any related studies. Included studies are categorized by the drug and/or class of drug examined in a particular study. These include studies that examined the efficacy of modafinil (or armodafinil), sodium oxybate, antidepressants, and/or amphetamines (or other similar stimulants). The efficacy of each drug and/or drug class is discussed separately in the four subsections that follow.

Table 22: Included Studies

Primary Reference	Year	Other Relevant References	Drug or Drug Class			
			Amphetamines	Modafinil or Armodafinil	Antidepressant	Sodium Oxybate
Saletu et al.	2009			✓		
Joo et al.	2008			✓		
Black & Houghton	2006			✓		✓
Harsch et al.	2006			✓		
Xyrem International Study Group	2005a	Xyrem International Study Group, 2005b Weaver et al., 2006				✓
Saletu et al.	2004			✓		
Schwartz et al.	2004	Schwartz et al., 2005		✓		
Mayer et al.	2003				✓	
Schwartz et al.	2003	Schwartz et al., 2005		✓		
Thorpy et al.	2003			✓		
U.S. Xyrema Multicenter Study Group	2002	U.S. Xyrema Multicenter Study Group, 2003a U.S. Xyrema Multicenter Study Group, 2003b U.S. Xyrema Multicenter Study Group, 2004 Thorpy et al., 2004				✓
USMNMSG (Study II)	2000	Mitler et al., 2000		✓		
USMNMSG (Study I)	1998	Mitler et al., 2000		✓		
Broughton et al.	1997	Moldofsky et al., 2000		✓		
Mayer et al.	1995				✓	
Reinish et al.	1995				✓	
Hublin et al.	1994				✓	
Boivin et al.	1993			✓		
Mitler et al.	1993		✓			
Lammers et al.	1991				✓	
Guilleminault	1986				✓	
Mitler et al.	1986		✓			
Shrader et al.	1986				✓	
Shindler et al.	1985		✓			
Schachter and Parks	1980				✓	
TOTALS			**3**	**12**	**8**	**3**

Key Question 2A: What is the Impact of Treatment with Modafinil or Armodafinil for Narcolepsy on Driver safety?

In this subsection we examine the available evidence pertaining to the efficacy of modafinil (or armodafinil) for the treatment of narcolepsy (with or without cataplexy). As described in Section 1 and

the beginning of this section, modafinil is currently the first line drug in the treatment of EDS associated with narcolepsy.

Study Design Characteristics

Design details of the 12 studies that examined the impact of treatment of individuals with modafinil or armodafinil on outcomes relevant to driver safety are presented in Table 23. Eleven of the 12 included studies were randomized controlled trials. Seven included studies used a cross-over design in which all individuals acted as their own controls (the order in which each individual received the active drug or placebo was randomized). The remaining five studies used parallel treatment arms in which enrollees were randomly assigned to a single treatment group. Three of the latter studies were multicenter studies that enrolled over 200 individuals with narcolepsy. Ten of the included studies were double-blind while one was single-blinded, and one study was not blinded at all.

While each included study was controlled, not all studies (k=3) utilized a placebo control. This is because the objective of all 12 studies was not identical. Nine included studies were placebo controlled trials designed to assess the safety and efficacy of modafinil among individuals with narcolepsy, two studies were designed to examine the impact of different dosing regimens (both dose and frequency of administration) on the efficacy and safety of modafinil, and one study was designed to assess the impact of changing the treatment of individuals with narcolepsy from methylphenidate over to modafinil.

Follow-up time was generally short with the longest follow-up period under experimental conditions being 12 weeks. Following the end of the study, individuals enrolled in two included studies (USMNMSG I and II) were offered the opportunity to enter an open-label observational study (Mitler et al., 2000). Enrollees in this follow-up study were all treated with modafinil and the long-term impacts of the drug were observed.

Table 23: Study Design Details – Studies of Modafinil and Armodafinil

Reference	Year	Study design	No. of centers	N =	Cross-over?	Blinding	Study Duration	Control	Treatment
Efficacy and Safety Studies									
Saletu et al.	2009	RCT with X-over	1	15	Yes	Double	7 wks 3 wk treatment phase 1 1 wk washout 3 wk treatment phase 2	Placebo Escalating dose - 1 capsule morning +1 capsule noon wk 1 - 2 capsules morning +1 capsule noon wk 2 - 2 capsule morning +2 capsules noon wk 3	Treatment 1 Modafinil – escalating dose –100 mg morning + 100 mg noon wk 1 – 200 mg morning + 100 mg noon wk 2 – 200 mg morning + 200 mg noon wk 3
Joo et al.	2008	CT	1	53	No	Single	4 wks 4 wk treatment phase	Placebo 1 dose/day	Treatment 1 Modafinil dose titrated – mean dose (SD) = 207.8 (62.3) mg/day
Black & Houghton	2006	RCT	44	270	No	Double	10 wks 2 wk modafinil only 8 wk treatment phase	Placebo Modafinil placebo +sodium oxybate placebo	Treatment 1 Modafinil (normal dose) +sodium oxybate (normal dose) Treatment 2 Modafinil placebo +sodium oxybate (normal dose) Treatment 3 Modafinil (normal dose) +sodium oxybate placebo
Harsch et al.	2006	RCT	47	196	No	Double	12 wks 12 wk treatment phase	Placebo 1 dose morning	Treatment 1 Armodafinil 150 mg morning Treatment 2 Armodafinil 250 mg morning

Reference	Year	Study design	No. of centers	N =	Cross-over?	Blinding	Study Duration	Control	Treatment
Saletu et al.	2004	RCT with X-over	1	16	Yes	Double	11 wks 3 wk treatment phase 1 1 wk washout 3 wk treatment phase 2 1 wk washout 3 wk treatment phase 3	Placebo 1 dose/day	Treatment 1 Modafinil 200 mg/day Treatment 2 Modafinil 300 mg/day Treatment 3 Modafinil 400 mg/day
USMNMSG (Study II)	2000	RCT	21	271	No	Double	11 wks + open label follow-up 9 wk treatment phase 2 wk discontinuation period	Placebo 1 dose morning	Treatment 1 Modafinil 200 mg morning Treatment 1 Modafinil 400 mg morning Open label follow-up Titrated dose at physicians discretion
USMNMSG (Study I)	1998	RCT	18	283	No	Double	11 wks + open label follow-up 9 wk treatment phase 2 wk discontinuation period	Placebo 1 dose morning	Treatment 1 Modafinil 200 mg morning Treatment 1 Modafinil 400 mg morning Open label follow-up Titrated dose at physicians discretion
Broughton et al.	1997	RCT with X-over	9	75	Yes	Double	6 wks 2 wk treatment phase 1 2 wk treatment phase 2 2 wk treatment phase 3	Placebo 1 dose morning + 1 dose night	Treatment 1 Modafinil 100 mg morning + 100 mg night Treatment 2 Modafinil 200 mg morning + 200 mg night
Boivin et al.	1993	RCT with X-over	1	10	Yes	Double	12 wks 2 wk run in 4 wk treatment phase 1 2 wk washout 4 wk treatment phase 2	Placebo 1 dose morning + 1 dose night	Treatment 1 Modafinil 200 mg morning + 100 mg night

Reference	Year	Study design	No. of centers	N =	Cross-over?	Blinding	Study Duration	Control	Treatment
Dosing Studies									
Schwartz et al.	2004	RCT with X-over	1	24	No	Double	5 wks 2 wk washout 3 wk treatment phase	NA	Treatment 1 Modafinil 400 mg morning only Treatment 2 Modafinil 400 mg morning + modafinil 200 mg noon
Schwartz et al.	2003	RCT with X-over	3	32	Yes	Double	12 wks 1 wk washout 3 wk treatment phase 1 1 wk washout 3 wk treatment phase 2 1 wk washout 3 wk treatment phase 3	NA	Treatment 1 Modafinil 200 mg morning only Treatment 2 Modafinil 400 mg morning only Treatment 3 Modafinil 200 mg morning + Modafinil 200 mg noon
Drug change studies (amphetamines to Modafinil or Armodafinil)									
Thorpy et al.	2003	RCT with X-over	1	40	No	No	5 wks 2 wk phase 1 1 wk phase 2 2 wk phase 3 (either no washout, 2 day washout, or 3 day taper between phase 1 and phase 2)	NA	Treatment 1 Methylphenidate (previously prescribed dose; phase 1) Modafinil 200 mg morning only (phase 2) Modafinil 400 mg morning only (phase 3)

CT = Controlled trial
NA = Not applicable
RCT = Randomized controlled trial
SD = Standard deviation
X-over = Cross-over

Characteristics of Enrollees

The purpose of this subsection is to provide details about the characteristics of patients included in each of these studies and the extent to which these individuals are: 1) generalizable to individuals with narcolepsy in the general population; and 2) are similar to CMV drivers in the United States. Enrollment criteria and baseline characteristics of the patients included in each of these studies are presented in Table 24.

In general, the populations in these studies contain approximately 50 percent males (range 37- to 58-percent males). In the majority of studies, the mean age was typically in the forties (range 29.1 to 48 years) and typically included patients whose age fell between 17 and 71 years. However, one study included a single individual 14 years of age. While this group may present some similarities to the population predominantly found among CMV drivers in the United States, we have no information regarding whether any of them were professional drivers, thus limiting our ability to generalize beyond factors such as age or gender.

In most studies, narcolepsy subjects were recruited from sleep disorder clinics and therefore, are representative of the narcolepsy population currently receiving treatment. While this most likely captures the majority of individuals with narcolepsy, it may not represent more mild cases (i.e., individuals who do not need routine treatment or who are undiagnosed). Diagnoses of narcolepsy in these studies were primarily based on accepted medical standards (e.g., ICDS and ICDS-2 diagnostic criteria, including medical history, clinical presentation, polysomnographic sleep study results). Mean ESS scores at baseline for included patients ranged from 15.3 to 17.5 (with a score of 10 or less considered normal). In addition, most patients presented at baseline with two or more SOREMPs. Sixty to 100 percent of patients included in these trials also presented with cataplexy. The presence of other associated symptoms (e.g., hypnogogic hallucinations, sleep paralysis, interrupted night sleep), were generally more variable.

Most studies excluded subjects (both cases and controls) with any evidence of a medical or psychiatric disorder that might account for or contribute to their EDS. Sleep apnea and any sleep disorder other than narcolepsy were also typically included as exclusion criteria. In the majority of studies, individuals were required to have symptoms that had stabilized two weeks to one month before the beginning of the study. In most cases, this included patients who had been receiving stable doses of one or more drugs for the treatment of narcolepsy (with or without cataplexy). In these studies, trials with modafinil (or armodafinil) were always preceded by a washout period or a period of being drug-free (two weeks to 30 days prior to trial entry).

The generalizability of the findings of the included studies to CMV drivers is unclear as none of the included studies examined narcolepsy specifically among CMV drivers. The mean age of participants included in these studies (typically in the 40's) is relatively comparable to the average age of CMV drivers (43 years); however, females were largely over-represented in these studies compared to the CMV driver population.

Table 24: Characteristics of Enrollees – Studies of Modafinil and Armodafinil

Reference	Year	Enrollment criteria	Baseline Pt Characteristics
Efficacy Studies			
Saletu et al.	2009	• ICD-10 diagnosis of narcolepsy • Symptoms were required to have been stable for 2 wks before the beginning of the study. All patients were suffering from EDS and recurrent daytime naps. • Excluded patients included: evidence of a medical or psychiatric disorder that might account for the primary complaint; patients with sleep apnea, restless legs syndrome (RLS) or periodic limb movement disorder; pregnant or lactating women; patients with a history of drug abuse or dependency, including alcohol; patients requiring psychoactive medication or unwilling to temporarily discontinue anticataplectic medication or any other drug that might interfere with the study assessments; patients who were unable or unwilling to comply with the protocol; patients who worked at night	• N=15; Mean age: 38 ±18years; M:F = 7:8 • Mean ESS = 17.3 (±4.0) • 10 patients had a clear cataplexy; 12 patients experienced hypnagogic hallucinations; 6 sleep paralysis. • Polysomnography mean sleep latency = 4.6 (±3.1) min; mean REM sleep latency of 27.0 (±41.1) min; Mean sleep efficiency index of 85% (±15.8). The mean apnea-hypopnea index was 4.2 (±4.5)/h of sleep, which excluded an obstructive sleep apnea syndrome as a possible cause of EDS. The mean arousal index was 15.9 (±10.0)/h of sleep; the PLM arousal index 1.6 (±2.8). In the MSLT, mean sleep latency was 4.3±1.9 min (range 1.33–7) and the number of sleep onset REM periods (SOREMPs) was at least 2 per patient out of 5 nap trials. HLA typing for DQB1*0602 was positive in 12 patients.
Joo et al.	2008	All patients suffered from narcolepsy with cataplexy (as defined in ICSD-2) and had no drug history for treatment of EDS or cataplexy	**Modafinil Group** • 32 narcolepsy patients (M:F = 16:16) • Mean age = 31.4 (14-47 years) • Mean ESS = 17.2 (±3.5) • Mean sleep latency = 3.8 (±2.9 min) • SOREMPs = 3.7 (±1.3) • Mean REM sleep latency = 2.6 (±2.3) **Placebo** • 21 narcolepsy patients (M:F = 11:10) • Mean age = 29.1 (15-42 years) • Mean ESS = 16.0 (±3.9) • Mean sleep latency = 4.6 (±2.8 min) • SOREMPs = 3.7 (±1.2) • Mean REM sleep latency = 2.9 (±2.6)
Black et al.	2006	• Adults (18 years or older) with diagnosis of narcolepsy (ICSD) • Were taking a stimulant medication for the treatment of EDS for at least 3 months and were taking stable doses of modafinil (200 to 600 mg/day) for at least 1 month immediately prior to the trial or were taking stable doses of modafinil for at least 6 wks prior to trial entry • No other active, clinically significant disorders or sleep disorder other than narcolepsy • No use of sodium oxybate or any investigational therapy within the 30-day period prior to enrollment	**SO/Placebo Modafinil** • 50 patients (M:F = 26:24) • Mean age = 35.1 (±12.9 years) **Placebo SO/Placebo Modafinil** • 55 patients (M:F = 24:31) • Mean age = 41.0 (±13.4 years) **Placebo SO/Modafinil** • 63 patients (M:F = 32:31) • Mean age = 38.9 (±15.6 years) **SO/Modafinil** • 54 patients (M:F = 25:29) • Mean age = 38.9 (±15.9 years)
Harsch et al.	2006	• Adults (18 years or older) with diagnosis of narcolepsy (ICSD) • No other active, clinically significant disorders or sleep disorder other than narcolepsy, and did not consume more than 600 mg/day of caffeine • Had no history of alcohol, narcotic, or other drug abuse, and didn't take any drugs or have any disorders that would interfere with drug absorption, distribution, metabolism, or excretion • Had no known sensitivity to stimulants or modafinil	**Placebo** • N = 63 patients (M:F = 32:31) • Mean age = 39.2 (SD = 12.0 years) • CGI-S, n (%) – Moderately ill = **Armodafinil (150 mg)** • N = 64 patients (M:F = 28:36) • Mean age = 40.4 (SD = 12.5 years) • CGI-S, n (%) – Moderately ill = **Armodafinil (250 mg)** • N = 67 patients (M:F = 25:42) • Mean age = 35.0 (SD = 12.5 years) • CGI-S, n (%) – Moderately ill =

Reference	Year	Enrollment criteria	Baseline Pt Characteristics		
		• Was able to complete self-rating scales and computer-based testing • Patients with self-reported cataplexy on stable doses of anticataplectic medications other than sodium oxybate were permitted to participate in the study	18 (29%) – Markedly ill = 34 (54%) – Severely ill = 11 (17%) – Most extremely ill = 0 (0%) • Mean MSLT = 2.6 min (SD = 1.5) • Cataplexy (%) = 65% • Mean MWT (0900-1500) = 12.5 min (SD = 6.6) • Mean MWT (1500-1900) = 12.9 min (SD = 6.6) • Mean ESS = 17.5 (SD = 3.9) • Mean BFI, global fatigue = 5.7 (SD = 2.1) • Mean BFI, worst fatigue = 7.9 (SD = 2.3)	19 (30%) – Markedly ill = 32 (50%) – Severely ill = 11 (17%) – Most extremely ill = 2 (3%) • Mean MSLT = 2.7 min (SD = 2.1) • Cataplexy (%) = 69% • Mean MWT (0900-1500) = 12.1 min (SD = 6.6) • Mean MWT (1500-1900) = 12.2 min (SD = 6.8) • Mean ESS = 17.3 (SD = 3.4) • Mean BFI, global fatigue = 5.7 (SD = 2.1) • Mean BFI, worst fatigue = 7.8 (SD = 2.2)	25 (37%) – Markedly ill = 29 (43%) – Severely ill = 12 (18%) – Most extremely ill = 1 (1%) • Mean MSLT = 2.8 min (SD = 1.9) • Cataplexy (%) = 66% • Mean MWT (0900-1500) = 9.5 min (SD = 6.1) • Mean MWT (1500-1900) = 10.5 min (SD = 6.6) • Mean ESS = 15.7 (SD = 4.7) • Mean BFI, global fatigue = 5.5 (SD = 1.9) • Mean BFI, worst fatigue = 7.7 (SD = 2.2
Saletu et al.	2004	• 16 patients with ICD-10 diagnosis of narcolepsy • Symptoms were required to have been stable for 2 wks before the beginning of the study • No other active, clinically significant disorders or sleep disorder other than narcolepsy • No history of drug abuse or dependency	• Mean age: 39.1 ±13. (21-59 years)		
USMNMSG (Study II)	2000	• Adult (17 years and older) with diagnosis of narcolepsy (ICSD) • History of EDS with or without cataplexy. • Objective documentation of sleepiness with the MSLT (mean latency of 8 minutes or less) • Two or more SOREMPs. • No other active, clinically significant disorders or sleep disorder other than narcolepsy	**Placebo** • N = 93 patients (M:F = 43:50) • Mean age = 41 (17-66 years) • Years since 1st symptoms = 24.8 (15.7) • Years since diagnosis	**Modafinil (200 mg)** • N = 89 patients (M:F = 37:52) • Mean age = 42 (18-67 years) • Years since 1st symptoms = 21.8 (14.5) • Years since diagnosis	**Modafinil (400 mg)** • N = 89 patients (M:F = 44:55) • Mean age = 42 (18-66 years) • Years since 1st symptoms = 22.0 (14.8) • Years since diagnosis

Reference	Year	Enrollment criteria	Baseline Pt Characteristics		
			= 8.1 (11.4) • Daytime sleep attacks = 85 (91%) • Cataplexy = 70 (75%) • Hypnogogic hallucinations = 66 (71%) • Sleep paralysis = 56 (60%) • Interrupted night sleep = 69 (74%)	= 7.6 (10.8) • Daytime sleep attacks = 83 (93%) • Cataplexy = 63 (71%) • Hypnogogic hallucinations = 49 (55%) • Sleep paralysis = 43 (48%) • Interrupted night sleep = 63 (71%)	= 6.6 (9.2) • Daytime sleep attacks = 87 (98%) • Cataplexy = 63 (71%) • Hypnogogic hallucinations = 50 (56%) • Sleep paralysis = 49 (55%) • Interrupted night sleep = 61 (69%)
USMNMSG (Study I)	1998	• Adult (18 years and older) with diagnosis of narcolepsy (ICSD) • History of recurrent daytime naps or lapses into sleep occurring almost daily for at least 3 months • Cataplexy, excessive somnolence or sudden muscle weakness plus associated features of sleep paralysis, hypnogogic hallucinations, automatic behaviors, disrupted major sleep episode • Objective documentation of sleepiness with the MSLT (mean latency of 8 minutes or less) • Two or more SOREMPs. • No other active, clinically significant disorders or sleep disorder other than narcolepsy • No prior adverse reaction to CNS stimulants	**Placebo** • N = 92 patients (M:F = 42:50) • Mean age = 42 (18-68 years) • Years since 1st symptoms = 22 (12.2) • Years since diagnosis = 7.3 (9.6) • Daytime sleep attacks = 87 (95%) • Cataplexy = 83 (90%) • Interrupted night sleep = 66 (72%) • Hypnogogic hallucinations = 62 (67%) • Sleep paralysis = 60 (65%)	**Modafinil (200 mg)** • N = 96 patients (M:F = 44:52) • Mean age = 40 (18-67 years) • Years since 1st symptoms = 21 (14.6) • Years since diagnosis = 8.8 (9.5) • Daytime sleep attacks = 92 (96%) • Cataplexy = 86 (90%) • Interrupted night sleep = 70 (73%) • Hypnogogic hallucinations = 64 (67%) • Sleep paralysis = 62 (65%)	**Modafinil (400 mg)** • N = 95 patients (M:F = 43:52) • Mean age = 44 (19-67 years) • Years since 1st symptoms = 23.2 (15.4) • Years since diagnosis = 9.7 (11.5) • Daytime sleep attacks = 90 (95%) • Cataplexy = 81 (85%) • Interrupted night sleep = 66 (69%) • Hypnogogic hallucinations = 69 (73%) • Sleep paralysis = 59 (62%)

Reference	Year	Enrollment criteria	Baseline Pt Characteristics	
Broughton et al.	1997	• Adult patients with a current diagnosis of narcolepsy (ICSD) including moderate or severe daytime sleepiness producing a moderate or marked impairment of social or occupational function. • Both newly and previously diagnosed patients included • No other active, clinically significant disorders or sleep disorder other than narcolepsy	N = 75	
Boivin et al.	1993	• Adult patients with narcolepsy • At least two SOREMPs • MSLT <5 minutes • Discontinued use of psychostimulants and anticataplectic medication for at least 2 wks before entering study • No other active, clinically significant disorders or sleep disorder other than narcolepsy	N = 10 Mean age = 45.6 (±3.1 ; 31-61years) M:F = 4:6	
Dosing Studies				
Schwartz et al.	2004	• Current diagnosis of narcolepsy confirmed by nocturnal polysomnography and the MSLT • Patients also reported a positive therapeutic response to modafinil but had residual late afternoon or evening sleepiness, with a CGI-S rating of 4 (at least moderately ill) with respect to late-day sleepiness at the screening visit • Patients excluded if they had a habitual wake-up time after 8 AM; an active, clinically significant medical disorder; other disorder(s) as the primary cause of excessive sleepiness; >10 apnea/hypopnea events/hour of sleep; a mean MWT time of >12 minutes across the first 4 sessions at baseline; daily consumption of8 cups of coffee or beverages/food amounting to 500 mg of caffeine; or a requirement for prohibited medications (e.g., tricyclic antidepressants, methylphenidate, amphetamines, pemoline, antipsychotic agents, monoamine oxidase inhibitors, benzodiazepines, anticonvulsants).	**Modafinil 400 mg/once daily** • N = 12 (M:F = 7:5) • Mean age 40 (18-61 years) • Mean MWT, min (range) = 6.5 (1.8-16.3) • CGI-S, N (%) – Markedly ill = 1 (8%) – Severely ill = 8 (67%) – Among the most extremely ill = 3 (25%) • Mean WCST (±SEM) = 18.5 (4.8) • Mean modafinil dose at screening, mean (range) = 400 mg (400 mg – 400 mg)	**Modafinil 600 mg/split dose** • N = 12 (M:F = 7:5) • Mean age 45 (14-60 years) • Mean MWT, min (range) = 6.6 (2.0-13.7) • CGI-S, N (%) – Markedly ill = 2 (17%) – Severely ill = 7 (58%) – Among the most extremely ill = 3 (25%) • Mean WCST (±SEM) = 22.3 (4.7) • Mean modafinil dose at screening, mean (range) = 417 mg (400 mg – 600 mg)
Schwartz et al.	2003	• Adult patients with a current diagnosis of narcolepsy • No other active, clinically significant disorders	Mean age = 43 years (28-61) 200 mg QD; MWT = 10.5 (10.21); ESS = 17.3 (3.17) 47years (28-71) 400 mg QD; MWT = 16.8 (11.12); ESS = 15.6 (1.8) 39 years (19-60) 400 mg SD; MWT = 9.9 (8.36); ESS = 15.3 (2.67)	

Reference	Year	Enrollment criteria	Baseline Pt Characteristics		
Drug change studies (amphetamines to Modafinil or Armodafinil)					
Thorpy et al.	2003	• Adult patients with a current diagnosis of narcolepsy • Previously treated with methylphenidate for at least 1 month • No other active, clinically significant disorders	**No washout** • N = 12 patients (M:F = 5:7) • Mean age = 35 (18-59 years) • Mean does of methylphenidate = 45 mg/day (SD = 11)	**Washout** • N = 14 patients (M:F = 7:7) • Mean age = 40 (17-65 years) • Mean does of methylphenidate = 37 mg/day (SD = 15)	**Taper Down** • N = 14 patients (M:F = 8:6) • Mean age = 48 (28-63 years) • Mean does of methylphenidate = 32 mg/day (SD = 11)

BFI = Brief Fatigue Inventory
CGI-S = Clinical Global Impression of Severity
EDS = Excessive daytime sleepiness
ESS = Epworth Sleepiness Scale
HLA DR 15/DQ*0602 = Antigens/genetics associated to narcolepsy
ICD-10 = International Classification Disease, 10th Edition
ICSD-2 = International Classification of Sleep Disorders
M:F = Male to female ratio
MSLT = Mean Sleep Latency Test
MWT = Maintenance of Wakefulness Test (measured in min)
PLM = Periodic limb movements
REM = Rapid eye movement
RLS = Restless leg syndrome
SD = Standard deviation
SO = Sodium oxybate
SOREMP = Sleep onset REM periods
USMNMSG = U.S. Modafinil in Narcolepsy Multicenter Study Group
WCST = Wisconsin Card Sort Test

Quality of Included Studies

The results of our assessment of the quality of the studies included in the present evidence base are presented in Appendix F and summarized in Table 25. As previously described, these studies fell into one of two categories: parallel group controlled trials, in which each subject is exposed to only one treatment, or crossover controlled trials, in which participants are assigned to a particular sequence of treatments, and therefore, are exposed to all of the treatments in a study.

The quality of studies found in our evidence base varied from "Moderate" to "High". "High" quality studies generally consisted of double blind randomized controlled trials (RCT), in which participants were randomly assigned to treatment groups and neither the participants or the researchers knew which treatment group the participant was assigned. RCTs are usually of higher quality than other studies because random assignment controls for both known and unknown confounding factors. Blinding adds additional protection against subjective bias on the part of the participant and researcher. The controlled trials rated as "Moderate" tended to lack blinding or had high rates of attrition.

Table 25: Quality of the Included Studies – Modafinil/Armodafinil

Reference	Year	Quality Scale Used	Quality Rating
Saletu et al.	2009	Quality Assessment Checklist for Crossover Controlled Trials	High
Joo et al.	2008	Quality Assessment Checklist for Controlled Trials	Low
Black & Houghton	2006	Quality Assessment Checklist for Controlled Trials	High
Harsh et al.	2006	Quality Assessment Checklist for Controlled Trials	Moderate
Saletu et al.	2004	Quality Assessment Checklist for Crossover Controlled Trials	High
Schwartz et al.	2004	Quality Assessment Checklist for Controlled Trials	High
Schwartz et al.	2003	Quality Assessment Checklist for Controlled Trials	Moderate
Thorpy et al.	2003	Quality Assessment Checklist for Controlled Trials	Moderate
U.S. Modafinil in Narcolepsy Multicenter Group (Study II)	2000	Quality Assessment Checklist for Controlled Trials	High
U.S. Modafinil in Narcolepsy Multicenter Group (Study I)	1998	Quality Assessment Checklist for Controlled Trials	High
Broughton et al.	1997	Quality Assessment Checklist for Crossover Controlled Trials	High
Boivin et al.	1993	Quality Assessment Checklist for Crossover Controlled Trials	High

Findings

The outcomes addressed by the studies that examined the efficacy of modafinil or armodafinil and the measures used to assess these outcomes are presented in Table 26.

Table 26: Outcomes Assessed and Measures Used – Studies of Modafinil and Armodafinil

Reference	Year	Study Design	Outcomes Assessed				
			Crash	Driving ability	Cataplexy	EDS	Cognitive and Psychomotor Performance
Efficacy studies							
Saletu et al.	2009	RCT	-	-	-	ESS, MWT	-
Joo et al.	2008	CT	-	-	-	ESS, MSLT	-
Black & Houghton	2006	RCT	-	-	-	ESS, MWT*	-
Harsch et al.	2006	RCT	-	-	-	BFI, ESS, MWT*	-
Saletu et al.	2004	RCT				ESS, MSLT	-
USMNMSG (Study II)	2000	RCT	-	-	-	ESS, MSLT*, MWT	-
USMNMSG (Study I)	1998	RCT	-	-	-	ESS, MSLT, MWT*	-
Broughton et al.	1997	RCT	-	-	-	ESS, MWT	FCRTT
Boivin et al.	1993	RCT	-	-	-	Number of daytime sleepiness events – self-reported	FCRTT
Impact of different dosing regimens							
Schwartz et al.	2004	RCT				MWT*	WCST*
Schwartz et al.	2003	RCT	-	-	-	ESS, MSLT, MWT*	-
Impact of changing from amphetamines to modafinil or armodafinil							
Thorpy et al.	2003	RCT	-	-	-	ESS*	-
TOTALS			0	0	0	12	3

*Primary outcome measure for study
BFI = Brief Fatigue Inventory
CT = Controlled trial
EDS = Excessive daytime sleepiness
ESS = Epworth Sleepiness Scale
FCRTT = Four Choice Reaction Time Test
MSLT = Mean Sleep Latency Test
MWT = Maintenance of Wakefulness Test
RCT = Randomized control trial
USMNMSG = U.S. Modafinil in Narcolepsy Multicenter Study Group
WCST = Wisconsin Card Sort Test

Direct Evidence – Impact of Modafinil (or Armodafinil) on Crash

None of the 12 included studies assessed the impact of modafinil or armodafinil on reducing crash risk. Consequently, one cannot determine whether individuals with narcolepsy (with or without cataplexy) who were treated with armodafinil or modafinil can be considered to be safe drivers (that is, they are at no greater risk for a crash than comparable individuals without the disorder). Given this, the best that one can do with the present evidence base is determine whether it is at all *plausible* that individuals with narcolepsy who are treated with modafinil or armodafinil may be considered safe to drive by looking at the impact of the treatment on risk factors that are known to be associated with sudden incapacitation (cataplexy events), and increased crash risk (simulated driving performance, EDS, or decreased cognitive and psychomotor function).

Indirect Evidence – Impact of Modafinil or Armodafinil on Driving Performance (Simulated or Closed Course) Studies, or Studies of Symptoms Associated with Crash Risk

None of the included studies examined the impact of modafinil (or armodafinil) on cataplexy or driving performance (simulated or otherwise). Three studies examined the impact of the treatment on cognitive and psychomotor function, and all twelve included studies examined the impact of modafinil (or armodafinil) on EDS.

Impact of Modafinil or Armodafinil on EDS

The findings of the 12 included studies that examined the impact of modafinil or armodafinil on EDS associated with narcolepsy are summarized in Table 27. The primary measures assessed in these studies were self-reported sleepiness as measured using the ESS and two polysomnographic sleep parameters, the MWT and MSLT.

The ESS score is a subjective measure of EDS that is derived from a simple questionnaire. The value of this instrument in providing a valid measure of EDS and as a predictor of crash risk is unclear. We consider this instrument because it is the most commonly used measure of EDS used today.

The MWT is a validated objective test for the evaluation of daytime somnolence/wakefulness (Arand et al., 2005). It assesses an individual's ability to remain awake while resisting the pressure to fall asleep during sleep inducing circumstances. MSLT is another validated objective test used to measure the tendency to fall asleep (Arand et al., 2005). The AASM has defined standardized protocols for both the MWT and MSLT in diagnosing sleep disorders, including narcolepsy (Littner et al., 2005). Details of each are presented in Appendix I.

Also shown for each study in the far right columns of Table 27 is whether or not modafinil (or armodafinil) improves patient performance for a given outcome relative to the control group, and whether or not improvements attain normal levels (as measured in individuals without narcolepsy).

Normative Data. For ESS, a normal score is typically considered to be a score of less than 10. Scores of 10 or more are considered abnormal sleepiness. For the MWT, normal values depend on trial duration (e.g., typically 20 min or 40 min protocols) as well as the definition of sleep. Definitions of sleep vary. In one study assessing normal values (Doghramji et al., 1997), sleep was defined as either: 1) first appearance of sleep (10 s of sleep or the first epoch of sleep), or 2) three continuous epochs of Stage 1 sleep or any single epoch of another sleep stage)-referred to as sustained. In this study, the mean values and lower limits for normality as assessed by two standard deviations lower than the mean for various MWT protocols were as follows:

Protocol	Mean	Lower limit (mean minus 2 SD)
Sustained MWT 40 min:	35.2 min	19.4 min
MWT 40 min:	32.6 min	12.9 min
Sustained MWT 20 min:	18.7 min	13.5 min
MWT 20 min:	18.1 min	10.9 min

In another study (Banks et al., 2004), sleep in the MWT was defined as to the first epoch of unequivocal sleep during the 40-minute trial. Mean latency in normal healthy subjects was 36.9 ± 5.4 (SD) minutes. The lower normal limit, defined as two standard deviations below the mean, was therefore 26.1 minutes. Mean sleep latency for the first 20 minutes of the trial (with sleep latency defined as time to the first appearance of one epoch of Stage 1 sleep or a 10-second microsleep) was 18.6 ± 2.3 minutes, with a lower normal limit of 14.0 minutes.

As for the MWT, normal values for the MSLT are similarly influenced by test protocol and definitions of sleep. In addition, age and total prior sleep time also affect scores on this test. Arand et al., (2005) systematically review MSLT scores for normal subjects collected from 77 articles. Of interest, the summary of data gathered from this review reveal that MSLT scores vary as a function of age, with latencies increasing with age. Normative data for protocols using four and five naps, with sleep defined as the first epoch of Stage 1 sleep are reported. The overall mean for four nap MSLT studies was 10.4 ±4.3 min. The overall means for five nap MSLT studies was 11.6 ±5.2 min. When looking at mean latencies as a function age, Arand et al., (2005) reported the following summary data:

Decade	Mean +SD	#Subjects
20s	10.1+4.9	255
30s	12.5+4.5	36
40s	12.2+1.2	20
50s	12.1+1.1	11
60s	11.2+5.2	54
80s	15.2+6.1	22

Table 27: Impact of Modafinil or Armodafinil on EDS

Reference	Year	Study Design	Measure	Findings	Evidence that drug improves outcome?	Evidence that drug improves outcome to normal?
Efficacy Studies						
Saletu et al.	2009	RCT	ESS	Overall group: ESS score improved significantly from 15.4 (± 4.0) under placebo to 10.2 (±4.1) under 400 mg modafinil (*P* = 0.004). Narcolepsy-cataplexy subgroup: ESS score improved significantly like from 15.7 (± 3.7) under placebo to 11.1 (+ 3.9) under 400 mg modafinil *(P* = 0.017).	Yes	No, on avg (normal <10) Yes for small number‡
			MWT (20 min)	Overall group: Latency to sleep increased nonsignificantly from 11.9 ± 6.9 min under placebo to 13.3 ± 7.1 min under modafinil Narcolepsy-cataplexy subgroup: latency to sleep increased nonsignificantly after modafinil treatment (12.3 ± 7.0 as compared with 10.5 ± 6.7 min under placebo).	Yes	Yes for small number†,‡
Joo et al.	2008	CT	ESS	Modafinil: ESS decreased from 20.3 ± 2.1 to 5.2 ± 3.1 *(P* < 0.01) Placebo: ESS did not change significantly after 4 wks (18.4 ± 3.9 to 16.3 ± 2.7)	Yes	Yes, on avg (normal <10)

Reference	Year	Study Design	Measure	Findings	Evidence that drug improves outcome?	Evidence that drug improves outcome to normal?
			MSLT (first 30-s epoch)	Modafinil: mean sleep latency was 10.7 ± 2.8 min (range 6–15) (paired t-test, *P*<0.001) Placebo: mean sleep latency was 5.9 ± 3.2 (range 3.5–9.0) (*P*=0.212).	Yes	Yes on avg¥
Black et al.	2006	RCT	ESS	Placebo: 16 to 16 (No change) SO/Placebo Modafinil: 15 to 12 (Change, *P*<0.001) Placebo SO/Modafinil: 14 to 15 (No change, *P=0*.767) SO/Modafinil: 15 to 11 (Change, *P*<0.001)	Yes	No, on avg (normal <10) Yes for small number‡
			MWT (20 min)	Placebo: 9.74 ± 6.57 at 2 wks to 6.87 ± 6.14 at 4 wks (Change = -2.72 ± 4.54 Placebo, NS) SO/Placebo Modafinil: 11.29 ± 6.40 at 2 wks to 11.97 ± 7.21 at 8 wks (Change = 0.58 ± 5.68; *P*<0.001) relative to placebo at 8 wks Placebo SO/Modafinil: 10.48 ± 6.03 at 2 wks to 9.86 ± 5.89 at 8 wks (Change = -0.53 ± 4.36; *P*=0.006) relative to placebo at 8 wks SO/Modafinil: 10.43 ± 6.77 at 2 wks to 13.15 ± 6.91 at 8 wks (Change = 2.68 ± 5.07; *P* <0.001) relative to placebo at 8 wks	Yes	Yes for small number†,‡
Harsch et al.	2006	RCT	BFI	Improvements in global fatigue for both treatment groups separately and the combined group at the final visit Mean ±SD change from baseline: – 150 mg/day, -1.5 ±2.14 (*P*=0.0007) – 250 mg/day, -1.3 ±2.09 (*P*=0.0018) – Combined group, -1.4 ±2.11 (*P*=0.0002) – Placebo, -0.3 ±1.89 There was a trend toward improvement from baseline for worst fatigue at the final visit but not significant (*P*<0.05)	Yes	Not determined
			ESS	Significant reductions for each armodafinil group compared with placebo at 8 wks (*P* <0.01 for all comparisons) and 12 wks (*P* <0.01) and at the final visit Mean ±SD increase from baseline: – 150 mg/day, -4.1 ±5.13, (*P* =0.0015) – 250 mg/day, -3.8 ±4.73, (*P*=0.0015) – Combined group, -3.9 ±4.91, (*P*=0.0006) At 4 wks there was a significant reduction for the 150 mg/day group (*P*=0.0402); 250 mg/day was not significant (*P*=0.0760) Final visit: 21% of 250 mg/day (*P*=0.0312) and 28% of the 150 mg/day (*P*=0.0023) had ESS scores of less than 10 compared with on 7% of patients in the placebo group	Yes	No, on avg (normal <10) Yes for small number‡

Reference	Year	Study Design	Measure	Findings	Evidence that drug improves outcome?	Evidence that drug improves outcome to normal?
			MWT (20 min)	MWT 0900-1500 sleep latency increased from baseline: – 150 mg/day, 1.3 min – 250 mg/day, 2.6 min – Combined group, 1.9 min – Placebo, -1.9 min (decreased from baseline) Relative to Placebo: – 150 mg/day, 3.2 min (*P* <0.01) – 250 mg/day, 4.5 min (*P* <0.01) – Combined group, 3.8 min (*P* <0.01) MWT 15900-1900 sleep latency increased from baseline: – 150 mg/day, 1.5 min – 250 mg/day, 1.6 min – Combined group, 1.6 min – Placebo, -1.2 min (decreased from baseline) Relative to Placebo: – 150 mg/day, 2.7 min (*P* <0.05) – 250 mg/day, 2.8 – Combined group, 2.8 min (*P* <0.05) The armodafinil groups, individually and collectively, had numerically longer MWT 1500-1900 sleep latencies when compared to placebo at 4, 8, and 12 wks, but the differences did not reach statistical significance	Yes	No†
Saletu et al.	2004	RCT	ESS	Decreased from a median of 14.5 after three wks of placebo to 12.5 after three wks of modafinil (*P*<0.05)	Yes	No, on avg (normal <10) Yes for small number‡
			MSLT	Latency to sleep stage S1 significantly increased from a median of 3.2 min after three wks of placebo to 6.6 min after three wks of modafinil (*P* <0.05)	Yes	No¥
USMNMSG (Study II)	2000	RCT	ESS	**Placebo**: Baseline (SD) = 17.6 (4.0) Wk 9 = 15.8 (4.8) (*P*<0.001) **Modafinil (200 mg)**: Baseline (SD) = 17.4 (3.8) Wk 9 = 13.0 (5.1) (*P*<0.001 compared to baseline & placebo) **Modafinil (400 mg):** Baseline (SD) = 18.0 (3.4) Wk 9 = 12.3 (5.1) (*P*<0.001 compared to baseline & placebo)	Yes	No, on avg (normal <10) Yes for small number‡
			MSLT	**Placebo**: Baseline (SD) = 2.2 (1.8) Wk 9 = 3.5 (3.4) (*P*<0.001 compared to baseline) **Modafinil (200 mg)**: Baseline (SD) = 3.0 (2.2) Wk 9 = 4.97 (4.3) (*P*<0.001 compared to baseline) **Modafinil (400 mg):** Baseline (SD) = 2.7 (2.0) Wk 9 = 5.1 (4.0) (*P*<0.001 compared to baseline & placebo)	Yes	No¥
			MWT (20 min)	**Placebo**: Baseline (SD) = 6.0 (5.0) Wk 9 = 5.5 (4.5) **Modafinil (200 mg)**: Baseline (SD) = 6.1 (4.9) Wk 9 = 8.2 (5.9) (*P*<0.001 compared to baseline & placebo)	Yes	No†

Reference	Year	Study Design	Measure	Findings	Evidence that drug improves outcome?	Evidence that drug improves outcome to normal?
				Modafinil (400 mg): Baseline (SD) = 5.9 (4.4) Wk 9 = 7.8 (5.3) (*P*<0.001 compared to baseline & placebo)		
USMNMSG (Study I)	1998	RCT	ESS	**Placebo**: Baseline (SD) = 18.3 (3.3) Wk3 = 16.8 (4.7) Wk 6 = 16.8 (4.8) Wk 9 = 17.1 (5.0)	Yes	No, on avg (normal <10) Yes for small number‡
				Modafinil (200 mg): Baseline (SD) = 17.9 (3.8) Wk3 = 14.0 (5.4) (*P*<0.001) Wk 6 = 13.9 (6.0) (*P*<0.001) Wk 9 = 14.4 (5.7) (*P*<0.001)		
				Modafinil (400 mg): Baseline (SD) = 17.1 (4.2) Wk3 = 12.6 (5.6) (*P*<0.001) Wk 6 = 12.6 (5.6) (*P*<0.001) Wk 9 = 13.0 (5.7) (*P*<0.001)		
			MSLT	**Placebo**: Baseline (SD) = 2.8 (2.2) Wk 9 = 3.3 (3.2)	Yes	No¥
				Modafinil (200 mg): Baseline (SD) = 2.9 (2.5) Wk 9 = 4.7 (4.4) (*P* <0.001)		
				Modafinil (400 mg): Baseline (SD) = 3.3 (2.9) Wk 9 = 5.2 (4.5) (*P*<0.001)		
			MWT (20 min)	**Placebo**: Baseline (SD) = 5.8 (4.7) Wk3 = 5.6 (4.5) Wk 6 = 5.4 (5.0) Wk 9 = 5.1 (4.7)	Yes	No†
				Modafinil (200 mg): Baseline (SD) = 5.8 (5.0) Wk3 = 8.1 (6.2) (*P*<0.001) Wk 6 = 8.4 (6.4) (*P*<0.001) Wk 9 = 8.1 (6.1) (*P*<0.001)		
				Modafinil (400 mg): Baseline (SD) = 6.6 (5.2) Wk3 = 9.2 (5.7) (*P*<0.001) Wk 6 = 9.0 (5.8) (*P*<0.001) Wk 9 = 9.0 (6.2) (*P*<0.001)		
Broughton et al.	1997	RCT	ESS	**Placebo**: 16.5 (±4.4)	Yes	No, on avg (normal <10) Yes for small number‡
				Modafinil (200 mg): 14.9 (±5.6) (*P*=0.018)		
				Modafinil (400 mg): 14.1 (±5.6) (*P*=0.0009)		
			MWT (40 min)	**Placebo**: 11.2 (±9.8 min) Latency to stage 1 (min) = 8.1 (±6.9)	Yes	No†
				Modafinil (200 mg): 15.7 (±12.6min) 40.4% longer compared to placebo Latency to stage 1 (min) = 10.3 (±8.2)		
				Modafinil (400 mg): 17.2 (±13.0 min) 53.6% longer compared to placebo Latency to stage 1 (min) = 10.3 (±8.7)		

Reference	Year	Study Design	Measure	Findings	Evidence that drug improves outcome?	Evidence that drug improves outcome to normal?
Boivin et al.	1993	RCT	Number of daytime sleepiness events – self-reported	Significant reduction in the number and duration of daytime sleep episodes in modafinil treated group compared to placebo: Placebo: number episodes = 1.7 (±0.4 SEM); 76.8 min (±22.0) Modafinil: number episodes = 1.3 (±0.2 SEM); 47.1 min (±10.1)	Yes	No
Impact of different dosing regimens						
Schwartz et al.	2004	RCT	MWT (30 min)	**Modafinil (400 mg) single dose:** • Baseline mean MWT overall (range) = 6.5 (1.8-16.3) • Baseline mean MWT 5-7pm = 10.6 (±9.7) • Mean change at 3 wks MWT = 10.7 (±2.1) (*P*<0.001) • Mean change at 3 wks MWT (5-7pm) = 3.8 (±2.4) **Modafinil (600 mg) split dose:** • Baseline mean = 6.6 (2.0-13.7) • Baseline mean MWT 5-7pm = 8.0 (±5.7) • Mean change at 3 wks = 6.2 (±1.9) (*P* <0.01) • Mean change at 3 wks MWT (5-7pm) = 10.6 (±9.7) (*P*<0.05 relative to change in 400 mg group)	Yes	Normative data for 30 min not available
Schwartz et al.	2003	RCT	ESS	• Improved for all three dosing regimens compared to baseline (*P*<.001) • Trend for larger effect in the 400 mg vs. 200 mg but not significant	Yes	Unclear Absolute values not provided
			MSLT	• Improved for all 3 dosing regimens compared to baseline (*P*<.001) ; • Largest change for the 400 mg compared to 200 mg (P<.05)	Yes	Unclear Absolute values not provided
			MWT (30 min)	• Improved for all 3 dosing regimens compared to baseline (*P*<.001) ; • Largest change for the 400 mg compared to 200 mg (P<.05)	Yes	Normative data for 30 min not available
Impact of changing from amphetamines to Modafinil or Armodafinil						
Thorpy et al.	2003	RCT	ESS	At the end of the study (day 35), the mean ESS total score was less than 12 for each treatment group. – No washout: Mean (SD) = 11.3 (5.3) – Washout: Mean (SD) = 8.2 (4.3) – Taper-down: Mean (SD) = 10.1 (5.3) *No baseline measures described	Yes	Yes for a small proportion ‡ (normal <10)

†Based on normative data from Doghramji et al., 1997, Banks et al., 2004, and Arand et al., 2005
‡Exact proportions could not be determined.
¥Based on normative data from Arand et al., 2005
BFI = Brief Fatigue Inventory
CGI = Clinical Global Impression
CT = Controlled trail
ESS = Epworth Sleepiness Scale
MSLT = Mean Sleep Latency Test
MWT = Maintenance of Wakefulness Test
NS = Not significant
RCT = Randomized controlled trial
SO = Sodium oxybate

As shown in the table above, in all of the studies examined, subjects in the modafinil (or armodafinil) treated groups showed evidence of improvement on all measures of daytime sleepiness (e.g., ESS, and latencies for the MSLT and MWT) compared either with placebo treated groups, or baseline values. There was also a dose-dependent response observed in studies that examined dosing effects (Schwartz et al., 2003 & 2004). When looking at the change in modafinil (or armodafinil) treated groups relative to normal values, in some instances, patients attained what are considered to be normal values, while most did not. For example, in only one study (Joo et al., 2008) did the ESS scores reach normal values on average post treatment (going from 20.3 ±2.1 at baseline to 5.2 ±3.1 after treatment). Scores for the ESS were often much higher than this in narcolepsy patients, even after treatment with modafinil. In most cases, the mean ESS score was over 10, which is considered to be abnormal sleepiness. However, in most studies, a small percentage of patients, typically on the order of 20% to 25% demonstrated scores that reached normal levels.

Likewise, when looking at latencies for the MSLT and the MWT, scores were improved (e.g., latencies lengthened) in all studies for treated groups compared to placebo and/or baseline. However, in most studies, values did not reach normal levels on average. Generally however, some unknown percentage of patients in a given study did reach normal levels. Although there is limited data available to determine which patients have more successful treatment, several studies did find that there is a dose-dependent response to treatment with modafinil and armodafinil. Other factors such as age and disease severity are also likely to play a role.

Also of interest, Black et al., (2006) compared combinations of active and placebo preparations of modafinil and sodium oxybate. Subjects who received active modafinil showed improvement in objective and subjective sleepiness compared to placebo modafinil. Those subjects receiving both active modafinil and active sodium oxybate showed the most improvement suggesting an additive effect of the combination of both modafinil and sodium oxybate.

Impact of Modafinil or Armodafinil on Cognitive and/or Psychomotor Function

Three of the 12 studies included in the modafinil/armodafinil evidence base examined the impact of modafinil on measures of cognitive and psychomotor function among individuals with narcolepsy. Two studies measured this outcome using the FCRTT and one study used the WCST. The findings of these studies are summarized in Table 28.

Table 28: Impact of Modafinil or Armodafinil on Cognitive and Psychomotor Function

Reference	Year	Study Design	Measure	Findings	Evidence that drug improves outcome?	Evidence that drug improves outcome to normal?
Efficacy Studies						
Broughton et al.	1997	RCT	FCRTT	No differences in the mean daily reaction time or the number of gaps. Compared with placebo, there was an 11% decrease in errors on modafinil 200 mg (P=0.50) and a 20% decrease on modafinil 400 mg (P=0.074). During the last session, after the second dose of modafinil	No	No

Reference	Year	Study Design	Measure	Findings	Evidence that drug improves outcome?	Evidence that drug improves outcome to normal?
				(corresponding to its maximal plasma concentration) performance improved on both doses of modafinil compared to placebo. The number of gaps reduced by 41% (*P*=0.026) and 44% (*P*=0.027) in the 200 mg and 400 mg groups, respectively.		
Boivin et al.	1993	RCT	FCRTT	A reduction of mean reaction time was observed but difference not statistically significant. Placebo: reaction time (ms) = 480 (±40 SEM); 76.8 min (±22.0); # gaps = 23 (±8) Modafinil: reaction time (ms) = 449 (±28SEM); 47.1 min (±10.1) (*P*=0.08); # gaps = 16 (±5)	No	No
Impact of different dosing regimens						
Schwartz et al.	2004	RCT - Dose	WCST	Combined (400 mg single dose and 600 mg split dose) Mean (± SEM) total number of errors: decreased from 20.4 ± 3.3 at baseline to 12.3 ± 1.5 at 3 wks post treatment (*P*<0.05). Mean (± SEM) total percent errors : decreased from 20.0 ± 2.3 at baseline to 14.1 ± 1.0 at 3 wks post treatment (*P*<0.05)	Yes	No

FCRTT = Four Choice Reaction Time Test
RCT = Randomized controlled trial
SEM = Standard error of mean
WCST = Wisconsin Card Sort Test

While all three studies found that modafinil improved cognitive function in individuals with narcolepsy, only one study found this improvement to be statistically significant. None of the studies provide evidence to support the contention that individuals with narcolepsy who are treated with therapeutic doses of modafinil will demonstrate improvements in cognitive or psychomotor function to the extent that these functions may be considered normal.

Summary of Findings

Direct Evidence – Crash Studies:

- **Evidence-based conclusions pertaining to the impact of treatment with modafinil or armodafinil on crash risk among individuals with narcolepsy cannot be drawn at this time.**

No studies that directly examined the impact of treatment with modafinil or armodafinil on crash risk were identified by our searches.

Indirect Evidence: Driving Performance (Simulated or Closed Course) Studies, Studies of Symptoms Associated with Crash Risk:

- **Evidence-based conclusions pertaining to the impact of treatment with modafinil or armodafinil on driving performance among individuals with narcolepsy cannot be drawn at this time.**

No studies that examined the impact of treatment with modafinil or armodafinil on driving performance were identified by our searches.

- **Modafinil and armodafinil are effective in improving symptoms of EDS (as measured using ESS scores and sleep latencies for the MSLT and MWT in patients with narcolepsy. However, improvements do not attain normal levels in the majority of patients (Strength of Evidence: Strong).**

Twelve studies evaluated outcomes related to daytime sleepiness in patients with narcolepsy (both with and without cataplexy). Ten studies (Quality Rating: one "Low", three "Moderate", and six "High") assessed the use of modafinil (or armodafinil) on ESS scores. In all 10 studies, ESS scores were improved. Post treatment scores were typically between 11 and 14.

Ten studies (Quality Rating: one "Low", two "Moderate", and seven "High") also examine the efficacy of modafinil (or armodafinil) on sleep latency measured with either the MSLT and/or the MWT. Again, in all cases, latencies were improved following treatment with modafinil (or armodafinil). In addition, in studies that examine dose responses, there was clear evidence of a dose-dependent response. However, on average, latencies did not reach normal values.

In summary, there is clear and robust evidence that treatment with modafinil or armodafinil is effective in reducing daytime sleepiness associated with narcolepsy; however, the majority of patients do not reach normal levels.

- **Evidence-based conclusions pertaining to the impact of treatment with modafinil or armodafinil on cognitive and psychomotor performance among individuals with narcolepsy cannot be drawn at this time.**

Currently available evidence is mixed with respect to the impact of modafinil on cognitive factors. Three studies (Quality Rating: "High") examined cognitive function (using variable measures) of patients treated with modafinil. In two studies that used the FCRTT, no evidence of improvement was evident following treatment with modafinil. However, one study showed significant reductions in errors on the WCST.

Key Question 2B: What is the Impact of Treatment with Sodium Oxybate for Narcolepsy on Driver Safety

In this subsection we examine the available evidence pertaining to the efficacy of sodium oxybate for the treatment of narcolepsy (with or without cataplexy). As described in Section 1 and the beginning of this section, sodium oxybate is currently the first line drug in the treatment of cataplexy associated with narcolepsy. In the United States, it is also indicated for the treatment of EDS and disrupted sleep due to narcolepsy.

Study Design Characteristics

As noted above, our searches identified three independent studies of the impact of sodium oxybate among individuals with a diagnosis of narcolepsy (with or without cataplexy) on outcomes relevant to driver safety. Design details of these three independent studies that examined the efficacy of treatment

of individuals with narcolepsy with sodium oxybate on outcomes relevant to driver safety are summarized in Table 29.

Table 29: Study Design Details – Studies of Sodium Oxybate

Reference	Year	Study design	No. of centers	N =	Cross-over?	Blinding	Study Duration	Control	Treatment
Efficacy Studies									
Black & Houghton	2006	RCT	44	270	No	Double	10 wks 2 wk modafinil only 8 wk treatment phase	Placebo Modafinil placebo +sodium oxybate placebo	Treatment 1 Modafinil (normal dose) +sodium oxybate Treatment 2 Modafinil placebo +sodium oxybate Treatment 3 Modafinil (normal dose) +sodium oxybate placebo
Dosing and Efficacy Studies									
Xyrem International Study Group	2005	RCT	42	228	No	Double	16-17 wks 2 wk prebaseline phase 1 3 wk withdrawal of drugs for cataplexy phase 2 5 days (or 5 times half-life of discontinued drug up to 18 days) washout phase 3 2-3 wk baseline with placebo (single blind) phase 4 4 wk titration of treatment phase 5 4 wk of stable dose treatment phase 6	Placebo 3 groups comparable to treatment groups with titration of placebo: split 2x night dose (at bedtime and 2.5-4 hours later)	Treatment 1 Sodium Oxybate 4.5 g/day, split 2x night dose (at bedtime and 2-4 hours later) Treatment 2 Sodium Oxybate 6.0 g/day, split 2x night dose (titrated to maximal dose at 1.5 mg wk from wk 1; max dose reached wk 2) Treatment 3 Sodium Oxybate 9 g/day, split 2x night dose (titrated to maximal dose at 1.5 mg wk from wk 1; max dose reached wk 4)
U.S. Xyrema multicenter study group#	2002	RCT	Multiple	136	No	Double	16-17 wks 4 wk withdrawal of drugs for cataplexy phase 1 5 days (or 5 times half-life of discontinued drug up to 28 days) washout phase 2 2-3 wk baseline phase 3 4 wk of stable dose treatment phase 4 (no titration)	Placebo 3 groups comparable to treatment groups: split 2x night dose (at bedtime and 2.5-4 hours later)	Treatment 1 Sodium Oxybate 3 g/day, split 2x night dose at bedtime and 2-4 hours later) Treatment 2 Sodium Oxybate 6.0 g/day, split 2x night dose Treatment 3 Sodium Oxybate 9.0 g/day, split 2x night dose

Patients were permitted to remain on stimulant medications provided stable doses were used beginning five days prior to baseline and continuing until the end of the trial.

RCT = Randomized controlled trial

Characteristics of Enrollees

The purpose of this subsection is to provide details about the characteristics of patients included in the studies of sodium oxybate and the extent to which these individuals are: 1) generalizable to individuals with narcolepsy in the general population; and 2) are similar to CMV drivers in the United States. Enrollment criteria and baseline characteristics of the patients included in each of these studies are presented in Table 30.

Of the three studies included, 34.6 percent to 53 percent consisted of males. The mean age for treatment and comparison groups in this study ranged from 35.1 to 43.1 years, and included patients whose age fell between 16 and 75 years.

Narcolepsy subjects were recruited from sleep disorder clinics and therefore, are representative of the narcolepsy population currently receiving treatment. Diagnoses of narcolepsy, in these studies, were primarily based on accepted medical standards (e.g., ICDS diagnostic criteria). Mean or median ESS scores at baseline ranged from 15 to 19 (with a score of 10 or less considered normal). In addition, all patients in two trials (Xyrem International Study Group, 2005; U.S. Xyrema Multicenter Study Group, 2002) included only patients who presented with narcolepsy with cataplexy. Contrary to this, the Black et al., (2006) study did not exclude patients without cataplexy nor did this study examine the number of cataplexy events as an outcome measure.

Most studies excluded subjects (both cases and controls) with any evidence of a medical or psychiatric disorder that might account for or contribute to their condition. Sleep apnea and any sleep disorder other than narcolepsy were also typically included as exclusion criteria. In addition, all studies excluded individuals with occupations requiring variable shift work or routine night shifts.

Each of the studies included patients who had been receiving stable doses of one or more drugs for the treatment of narcolepsy. In two of the three studies, individuals taking prior stimulant drugs for EDS were permitted to continue taking their medication (e.g., modafinil, methylphenidate or other stimulant) throughout the trial period at stable doses. Both of these trials however were preceded by two to four weeks of being cataplectic drug-free. For the third study (Black et al., 2006) patients were required to have been taking a stimulant medication for the treatment of EDS for at least three months and were taking stable doses of modafinil (200 to 600 mg/day) for at least one month immediately prior to the trial or were taking stable doses of modafinil for at least six weeks prior to trial entry. All study participants were on stable doses of modafinil and took no sodium oxybate (or other anticataplectic drug) for two weeks prior to entering the double-blind phase of the trial.

The generalizability of the findings of the included studies to CMV drivers is unclear as none of the included studies examined narcolepsy specifically among CMV drivers. The mean age of participants included in these studies (typically in their 40's) is relatively comparable to the average age of CMV drivers (43 years); however, females were largely over-represented in these studies compared to the CMV driver population.

Table 30: Characteristics of Enrollees – Studies of Sodium Oxybate

Reference	Year	Enrollment criteria	Baseline Pt Characteristics			
Efficacy Studies						
Black & Houghton	2006	• Adults (18 years or older) with diagnosis of narcolepsy (ICSD) • Were taking a stimulant medication for the treatment of EDS for at least 3 months and were taking stable doses of modafinil (200 to 600 mg/day) for at least 1 month immediately prior to the trial or were taking stable doses of modafinil for at least 6 wks prior to trial entry • No other active, clinically significant disorders or sleep disorder other than narcolepsy. Also excluded were individuals with occupations requiring variable shift work or routine night shifts. • No use of sodium oxybate or any investigational therapy within the 30-day period prior to enrollment	**SO/Placebo Modafinil** • 50 patients (M:F = 26:24) • Mean age = 35.1 (±12.9 years)	**Placebo SO/Placebo Modafinil** • 55 patients (M:F = 24:31) • Mean age = 41.0 (±13.4 years)	**Placebo SO/Modafinil** • 63 patients (M:F = 32:31) • Mean age = 38.9 (±15.6 years)	**SO/Modafinil** • 54 patients (M:F = 25:29) • Mean age = 38.9 (±15.9 years)
Dosing and Efficacy Studies						
Xyrem International Study Group	2005	• Patients (16 years or older) with diagnosis of narcolepsy (ICSD) ○ Diagnostic criteria included an overnight polysomnogram and MSLT performed within the previous 5 years; current symptoms of narcolepsy, including EDS, cataplexy • No use of hypnotics, anxiolytics sedating antihistamines, anticonvulsants, or clonidine at the start of the baseline period • No other active, clinically significant disorders or sleep disorder other than narcolepsy • No current or recent history of a substance use disorder • No use of sodium oxybate or any investigational therapy within the 30-day period prior to enrollment • Not working in an occupation requiring variable shifts or routine night shifts	• 228 entered the double blind phase of the trial • M:F = 79:149 (34.6% vs. 65.4%) • Mean age = 40.5 years (range 16-75 • An analysis among the 3 dose groups and placebo group indicated that the patients were evenly distributed with respect to demographic parameters. • The study was completed by 209 of the 228 patients who entered the double blind treatment phase of the trial. While remaining on stimulant medications, ESS scores ranged from 17 to 19 (normal < 10) across the treatment groups and were essentially unchanged at the end of the baseline phase (Visit 5). Patients displayed median MWT scores ranging from 8.63 to 9.56 minutes in patients assigned to receive SO, while the median MWT score in patients assigned to receive placebo was 12.38 minutes. MWT results became more uniform at the end of the baseline period (Visit 5). 78% of patients were taking central nervous system stimulants for the treatment of EDS, the dose of these medications was held constant throughout the trial. – Modafinil (41.1%) – Methylphenidate (23.6%) – Dextroamphetamine (18.7%). 14% of patients were using a dextroamphetamine/amphetamine combination product for the treatment of obesity. Subsequent analysis revealed that the use of stimulant medications was uniformly distributed across placebo and active-drug groups (range, 74.6%-83.6%).			

Reference	Year	Enrollment criteria	Baseline Pt Characteristics			
U.S. Xyrema multicenter study group	2002	• Adults (18 years or older) with diagnosis of narcolepsy (ICSD) ○ Diagnostic criteria included a valid polysomnogram within the previous five years and a current diagnosis of narcolepsy for at least six months based on criteria established by the American Sleep Disorders Association • No other active, clinically significant disorders or sleep disorder other than narcolepsy • No substance abuse of risk of substance abuse • Excluded if taking medication for their narcolepsy other than a stable dose of stimulant for treating EDS • Not working in an occupation requiring variable shifts or routine night shifts.	**Placebo** • N = 34 patients	**3 g SO** • N = 34 patients	**6 g SO** • N = 33 patients	**9 g SO** • N = 35 patients
			• 136 patients enrolled in the study: • M:F = 57:79 (41.9% vs. 58.1%) • Mean age = 43.1 years • At baseline, the frequency of wkly cataplexy attacks ranged from 3-249 (median 21). • The study was completed by 120 (88%) patients. The demographics of each dose group were well balanced and there were no significant between-group differences except the 6 g group, which had a higher percentage of male (63.6%)			

EDS = Excessive daytime sleepiness
ESS = Epworth Sleepiness Scale
ICSD = International Classification of Sleep Disorders
M:F = Male to female ratio
MSLT = Multiple Sleep Latency Test
MWT = Maintenance of Wakefulness Test
SO = Sodium oxybate

Quality of Included Studies

The results of our assessment of the quality of the studies included in this evidence base are presented in Appendix F and summarized in Table 31. All three included studies were found to be of "High" quality.

Table 31: Quality of the Included Studies – Sodium Oxybate

Reference	Year	Quality Scale Used	Quality Rating
Black & Houghton	2006	Quality Assessment Checklist for Controlled Trials	High
U.S. Xyrem Multicenter Study Group	2002	Quality Assessment Checklist for Controlled Trials	High
Xyrema International Study Group	2005	Quality Assessment Checklist for Controlled Trials	High

Findings

The outcomes addressed by the studies that examined the efficacy of sodium oxybate and the measures used to assess these outcomes are presented in Table 32.

Table 32: Outcomes Assessed and Measures Used – Studies of Sodium Oxybate

Reference	Year	Study Design	Outcomes Assessed				
			Crash	Driving ability	Cataplexy	EDS	Cognitive and Psychomotor Performance
Efficacy Studies							
Black & Houghton	2006	RCT	-	-	-	ESS, MWT*	-
Impact of different dosing regimens							
Xyrem International Study Group	2005	RCT			% attacks	ESS, MWT*	-
U.S. Xyrema multicenter study group	2002	RCT	-	-	% attacks	ESS	-
TOTALS			0	0	2	3	0

*Primary outcome measure for study
ESS = Epworth Sleepiness Scale
MSLT = Mean Sleep Latency Test
MWT = Maintenance of Wakefulness Test
RCT = Randomized controlled trial

Direct Evidence – Impact of Sodium Oxybate on Crash

None of the three included studies assessed the impact of sodium oxybate on reducing crash risk.

Indirect Evidence – Impact of Sodium Oxybate on Driving Performance (Simulated or Closed Course) Studies, Studies of Symptoms Associated with Crash Risk

Three studies assessed the impact of sodium oxybate on symptoms of EDS. Two studies assessed the impact of sodium oxybate on symptoms of cataplexy. None of the included studies assessed the impact of sodium oxybate on any measures of cognitive or psychomotor function, or driving performance (simulated or otherwise).

Impact of Sodium Oxybate on Cataplexy

Table 33 shows the results of sodium oxybate on cataplexy attacks. In both studies which examined this outcome, cataplexy is measured as the self-reported number of attacks. In both studies, this outcome is

assessed as the percent change relative to placebo and/or baselines scores, for each of the different dosing levels.

Table 33: Impact of Sodium Oxybate on Cataplexy Attacks

Reference	Year	Study Design	Measure	Findings	Evidence that drug improves outcome?	Evidence that drug improves outcome to normal?
Impact of different dosing regimens						
Xyrem International Study Group	2005	RCT	Self reported # attacks	Median decreases compared to placebo: 4.5 g dose: 57.0% (*P*=0.003) 6.0 g dose: 65.0% (*P*=0.002) 9.0 g dose: 84.7% (*P*<0.001)	Yes	No
U.S. Xyrema multicenter study group	2002	RCT	Self reported # attacks	SO produced decrease in the reported frequency of cataplexy attacks. This change was significant across doses (*P*=0.0021) compared to baseline, representing a dose-related effect. Compared to baseline, median % change: • 3 g dose: 49.0% • 6 g dose: 49.0% • 9 g dose: 69.0% Compared to placebo: • 6 g dose (*P*=0.0529) • 9 g dose (*P*=0.0008)	Yes (9 g dose only)	No

RCT = Randomized controlled trial
SO = Sodium oxybate

Significant dose-dependent reductions in cataplexy were reported for 4.5 g, 6 g, and 9 g doses, with reductions in median number of cataplectic attacks of 57 percent, 65 percent, and 84.7 percent, respectively, compared with placebo. Another study reported significant improvement in cataplexy frequency at a dosage of 9 g/night only compared with placebo. Given that patients continued to experience cataplexy at all, it can be assumed that patients did not reach normal levels.

Impact of Sodium Oxybate on EDS

Table 34 shows findings from efficacy studies of sodium oxybate for the treatment of EDS associated with narcolepsy. The primary outcomes assessed in these trials were self-reported sleepiness as measured using the ESS, as well as polysomnographic sleep parameters such as MWT. Descriptions of these tests, along with normative values were presented above when describing the effect of modafinil (or armodafinil) on EDS.

Table 34: Impact of Sodium Oxybate on EDS

Reference	Year	Study Design	Measure	Findings	Evidence that drug improves outcome?	Evidence that drug improves outcome to normal?
Efficacy Studies						
Black & Houghton	2006	RCT	ESS	Placebo: 16 to 16 (No change) SO/Placebo Modafinil: 15 to 12 (Change, *P*<0.001)	Yes	No, on avg (normal <10)

Reference	Year	Study Design	Measure	Findings	Evidence that drug improves outcome?	Evidence that drug improves outcome to normal?
				Placebo SO/Modafinil: 14 to 15 (No change, *P*=0.767) SO/Modafinil: 15 to 11 (Change, *P*<0.001)		Yes for small number‡
			MWT	Placebo: 9.74 ± 6.57 to 6.87 ± 6.14 (Change = -2.72 ± 4.54 Placebo, NS) SO/Placebo Modafinil: 11.29 ± 6.40 to 11.97 ± 7.21 (Change = 0.58 ± 5.68; *P*<0.001) Placebo SO/Modafinil: 10.48 ± 6.03 to 9.86 ± 5.89 (Change = -0.53 ± 4.36; *P*=0.006) SO/Modafinil: 10.43 ± 6.77 to 13.15 ± 6.91 (Change = 2.68 ± 5.07; *P*<0.001)	Yes	Yes for small number†,‡
Impact of different dosing regimens						
Xyrem International Study Group	2005	RCT	ESS	Patients receiving SO reported dosed-related decreases in median ESS scores, which were significant at all doses compared with baseline values (for each, *P*<0.001). When compared with placebo, the median decrease in ESS scores was significant in the 6-g and 9-g dose groups (for each, *P*<0.001) at the end of the 8-wk study period. • 6 g dose: Median score decreased from 19 to 15 • 9-g dose: Median score decreased from 19 to 12	Yes (6 and 9 g dose)	No, on avg (normal <10) Yes for small number‡
			MWT	Patients receiving the 9-g dose displayed a robust median increase of more than10 minutes in the MWT, which was significant when compared with baseline as well as with placebo (for each, *P*<0.001), whereas there was no statistical change in the median MWT score in patients receiving the 6 g SO dose.	Yes (9 g dose)	Yes for some‡ (9 g dose)
U.S. Xyrema multicenter study group	2002	RCT	ESS	Improved in all of the SO treatment groups in a dose-related manner, becoming significant at the 9 g dose (*P*=0.0001) when compared to placebo. – Median score dropped from 17.0 to 12.0	Yes (9 g dose)	No, on avg (normal <10) Yes for small number‡

†Based on normative data from Doghramji et al., 1997, Banks et al., 2004, and Arand et al., 2005
‡Exact proportions could not be determined.
¥Based on normative data from Arand et al., 2005
*Primary outcome measure for study
ESS = Epworth Sleepiness Scale
MWT = Maintenance of Wakefulness Test
NS = Not significant
RCT = Randomized controlled trial
SO = Sodium oxybate

As shown in the table above, in all three of the studies examined, subject treated with sodium oxybate showed evidence of improvement on all measures of daytime sleepiness (e.g., ESS, and latencies for the MWT) compared either with placebo treated groups, or baseline values. For example, ESS scores at baseline in both groups ranged from 14-19 and were significantly reduced to 11-12 in each of the study groups. Latencies on the MWT were also significantly increased in two studies that examined this outcome. There was also a clear dose-dependent response observed in studies that examined dosing effects (Xyrem International Study Group, 2005 & U.S. Xyrema multicenter study group, 2002). Similar to the result observed for modafinil, when looking at the change in sodium oxybate treated groups relative to normal values, on average, treated groups did not reach normal levels. However, given the range of

standard deviations, it is clear that some small unknown proportion of patients in each trial did attain normal levels. Likewise, when looking at latencies for the MWT, scores were improved (e.g., latencies lengthened) in all three studies for treated groups compared to placebo and/or baseline. However, in most studies, values did not reach normal values on average.

Summary of Findings

Direct Evidence – Crash Studies:

- **Evidence-based conclusions pertaining to the impact of treatment with sodium oxybate on crash risk among individuals with narcolepsy cannot be drawn at this time.**

No studies that directly examined the impact of treatment with sodium oxybate on crash risk were identified by our searches.

Indirect Evidence: Driving Performance (Simulated or Closed Course) Studies, Studies of Symptoms Associated with Crash Risk:

- **Evidence-based conclusions pertaining to the impact of treatment with sodium oxybate on driving performance among individuals with narcolepsy cannot be drawn at this time.**

No studies that directly examined the impact of treatment with sodium oxybate on driving performance were identified by our searches.

- **Currently available evidence suggests that sodium oxybate is effective in improving self-reported symptoms of cataplexy in individuals with narcolepsy. However, treatment with the drug does not eliminate cataplexy entirely in the vast majority of patients (Strength of Evidence: High).**

Two studies (Quality Rating: "High") identified by our searches examined the efficacy of sodium oxybate in reducing cataplexy in patients with narcolepsy. Significant dose-dependent reductions in the median number of cataplectic attacks were observed in both trials compared with placebo and/or baseline. However, none of the studies found that sodium oxybate eliminated cataplexy entirely in the vast majority of treated individuals.

- **Currently available evidence suggests that sodium oxybate is effective in improving symptoms of EDS in individuals with narcolepsy. However, these improvements do not result in levels of daytime sleepiness that can be considered to be normal in the vast majority of individuals (Strength of Evidence: High).**

Three studies (Quality Rating: "High") examined the efficacy of sodium oxybate in treating EDS. Each of the three studies showed evidence of improvement on all measures of daytime sleepiness (e.g., ESS, and latencies for the MWT) compared either with placebo treated groups, or baseline values (two of which demonstrated dose-dependent improvements). However, in most studies, values did not reach normal values.

- **Evidence-based conclusions pertaining to the impact of treatment with sodium oxybate on cognitive and psychomotor function among individuals with narcolepsy cannot be drawn at this time.**

No studies that directly examined the impact of treatment with sodium oxybate on cognitive or psychomotor function were identified by our searches.

Key Question 2C: What is the Impact of Treatment with Antidepressants for Narcolepsy on Driver Safety?

In this subsection we examine the available evidence pertaining to the efficacy of antidepressants for the treatment of narcolepsy (with or without cataplexy). As described in Section 1 and the beginning of this section, antidepressants, including the tricyclic antidepressants, SSRIs, SNRIs, MAO-B inhibitors, and other similar drugs, are used largely to treat cataplexy and/or other associated symptoms of narcolepsy (e.g., hypnagogic hallucinations, sleep paralysis, interrupted night sleep, etc.). Some of these drugs are also used variably to treat EDS, the primary disabling symptom of narcolepsy.

Study Design Characteristics

Design details of the eight included studies that examined the impact of treatment with antidepressants on outcomes relevant to driver safety are presented in Table 35.

Table 35: Study Design Details – Studies of Antidepressants

Reference	Year	Study design	Number of centers	N =	Cross-over?	Blinding	Study Duration	Control	Treatment
Efficacy Studies									
Mayer	2003	RCT	Multicenter	126	No	Double	6 wks 2 wk baseline 4 wk treatment	Placebo	Treatment 1 Ritanserin 5 gm Treatment 2 Ritanserin 10 mg
Mayer et al.	1995	RCT	1	30	No	Double	4 wks 2 wk washout 2 day placebo 10 days treatment or placebo 2 day placebo	Placebo 2 doses per day	Treatment 1 Selegiline 5 mg (2x/d) Treatment 2 Selegiline 10 mg (2x/d)
Reinish et al.	1995	CT	1	22	No	No	Variable duration 2 wk washout 8-84 wk treatment group 4-300 wk comparison group	Control Group Methylphenidate 43 (±6.3) mg/d; split dose; 2/3 in morning, 1/3 at mid-day)	Treatment Selegiline 15-30 mg/d (mean dose =24 ±2.2 mg/d (split dose, morning and noon)
Hublin et al.	1994	RCT	1	17	Yes	Double	22 wks 2 wk washout 4 wk placebo 4 wk treatment 4 wk treatment 4 wk treatment 4 wk treatment	Placebo 4 tablets/d (2 at 8am, 1 at noon, 1 at 4pm)	Treatment 1 Selegiline 10 mg (4 tablets/d; active drug only at 8am, 1 tablet placebo, 1 tablet active) Treatment 2 Selegiline 20 mg (4 tablets/d; active drug only at 8am, 2 tablets) Treatment 3 Selegiline 30 mg (4 tablets/d; active drug at 8am and noon) Treatment 4 Selegiline 40 mg (4 tablets/d; active drug at 8am, noon and 4pm)
Lammers et al.	1991	RCT	1	28	No	Double	5 wks 1 wk washout 4 wk treatment	Placebo 2 doses per day	Treatment Ritanserin 2.5 mg 2x/d

Reference	Year	Study design	Number of centers	N =	Cross-over?	Blinding	Study Duration	Control	Treatment
Guilleminault et al.	1986	CT with X-over	1	22	Yes	Single	~10 wks 15 days washout 5 days placebo 6 wk full treatment 7 days reduced treatment 5 days placebo	Placebo 1 dose per day	Treatment Viloxazin 100 mg/d
Schrader et al.	1986	RCT	1	10	Yes	Double	13 wks 2 wk washout 1 wk run-in period 4 wk treatment or placebo 2 wk washout 4 wk alternative treatment or placebo	Placebo 2 doses per day	Treatment Femoxetine 300 mg 2x/d
Schachter and Parks	1980	RCT	1	18	Yes	Not stated	8 wks 1 wk washout 3 wk treatment 1 wk washout 3 wk alternative treatment	Placebo	Treatment 1 Fluvoxamine 50 mg 2x/d (adjusted to 25-200 mg/d) Treatment 2 Clomipramine 25 mg nightly (adjusted to 25-200 mg/d)

CT = Controlled trial
RCT = Randomized controlled trial
X-over = Crossover

Characteristics of Enrollees

The purpose of this subsection is to provide details about the characteristics of patients included in the antidepressant studies and the extent to which these individuals are: 1) generalizable to individuals with narcolepsy in the general population; and 2) are similar to CMV drivers in the United States. Enrollment criteria and baseline characteristics of the patients included in each of these studies are presented in Table 36.

Of the studies included in this subsection, most consisted of proportionally more males than females (typically 60 percent to 70 percent). The range of male participants was 23 percent in one study to 77 percent in another. The mean age for treatment and comparison groups in this study ranged from 43 to 53 years, and included patients whose age fell between 16 and 73 years. For the majority of these trials, however, the median age was in the mid forties.

As in the previous subsections, narcolepsy subjects were recruited from sleep disorder clinics and therefore, are representative of the narcolepsy population currently receiving treatment. In one study (Mayer, 2003), however, participants included both typical narcolepsy patients (with EDS, cataplexy, positive HLA-DR2 typing) as well as patients with atypical narcolepsy (e.g., EDS only or with one associated symptom, or cataplexy only along with negative HLA-DR2 typing). This study looked at the efficacy of ritanserin in treating symptoms other than EDS associated with narcolepsy. Similarly, Lammers et al. (1991), which also examined the efficacy of ritanserin did not require symptoms of cataplexy be present. In four studies, (Guilleminault et al., 1986; Hublin et al., 1994; Schachter and Parks, 1980; and Schrader et al., 1986), all included study participants were required to also have cataplexy. In two others (Mayer, et al., 1995; Reinish et al., 1995), 85 percent - 90 percent of patients presented with symptoms of cataplexy.

Most studies excluded subjects (both cases and controls) with any evidence of a medical or psychiatric disorder that might account for or contribute to their condition but fewer details were provided regarding other exclusionary criteria.

Each of the studies included patients who had been on doses of one or more drugs for the treatment of narcolepsy prior to entry in the study. In all but one case (Mayer, 2003) participants went through a one to two week washout period prior to starting the trial medication. In the Mayer (2003) study, participants continued taking their pretrial drugs at their established doses.

The generalizability of the findings of the included studies to CMV drivers is again, unclear as none of the included studies examined narcolepsy specifically among CMV drivers. The mean age of participants included in these studies (typically in the 40s) is relatively comparable to the average age of CMV drivers (43 years), and males made up a larger proportion of the study groups. But females were still over-represented in these studies compared to the CMV driver population in general.

Table 36: Characteristics of Enrollees – Studies of Antidepressants

Reference	Year	Enrollment criteria	Baseline Pt Characteristics	
Efficacy Studies				
Mayer	2003	Patients with Narcolepsy (ICSD); these included: • Patients with typical narcolepsy (e.g., EDS, cataplexy, positive HLA-DR2 typing) • Patients with atypical narcolepsy who had: a) EDS only or with one associated symptom (sleep paralysis, hypnogogic hallucinations, autonomic behavior); positive HLA-DR2 typing and positive MSLT (mean sleep latency < 5 min, two SOREMPs), or b) Cataplexy only, negative HLA-DR2 typing and positive MSLT • No other active, clinically significant disorders • No current or recent history of a substance use disorder • No shift work, irregular sleep/wake habits	Age rage 16 – 65 years Primary complaints at baseline: • Sleep attacks (40%) • EDS (37%) • Cataplexy (12%) Concurrent drug use at baseline and throughout trial: • Psychostimulant, N=76 • Antidepressant, N-66 (clomipramine, viloxazine) • GHB, N=6 • Benzodiazepines, N=7 • Drug-naïve, N=21	**Placebo** N=43; M:F = 25/18 Mean age = 40.9 (SD = ±14.2) Typical/Atypical/MSLT$_{neg}$ = 37/4/2 **Ritanserin, 5 mg** N=46; M:F = 29/17 Mean age = 43.2 (SD = ±12.5) Typical/Atypical/MSLT$_{neg}$ = 42/3/1 **Ritanserin, 10 mg** N=45; M:F = 30/15 Mean age = 43.2 (SD = ±15.0) Typical/Atypical/MSLT$_{neg}$ = 38/5/2
Mayer et al.	1995	• Adult patients between the ages of 16 and 65 years with Narcolepsy (as specified by Honda, 1986)	Mean age = 42.1 (17– 59 years) M:F = 23:7	**Placebo** N=10 M:F = 9/1 Mean age = 47.6 (SD = ±11.7) Cataplexy, N=8 **Selegiline, 2x 5 mg** N=10; M:F = 7/3 Mean age = 42.6 (SD = ±12.3) Cataplexy, N=10 **Selegiline, 2x 10 mg** N=10; M:F = 7/3 Mean age = 37.1 (SD = ±12.4) Cataplexy, N=9
Reinish et al.	1995	• Patients with narcolepsy	• N=22 (11 in treatment group; 11 in comparison group, age-matched to treatment group) • M:F = 5:6; Age range (17-63 years) • Cataplexy: 10/11 in treatment group • Previously treated with methylphenidate: 5/11 in treatment group	

Reference	Year	Enrollment criteria	Baseline Pt Characteristics
Hublin et al.	1994	• Patients with unequivocal narcolepsy diagnosis (ICSD)	• N=17 • M:F = 8:9; Median age=48 years; Age range (18-69 years) • Median duration of symptoms=28 years; Range (4-54 years) • Median age at onset=16; Range (7-30) • Cataplexy: 17/17 • SOREMPs: N=10 had 4; N=3 had 3; N=2 had 2; N=1 had 1 • Previously treated (N=11) • Mean Sleep stage 1 latency = 2 min • Mean sleep-onset latency = 2.1 min • All were HLA DR2-positive • Three patients had concomitant mild sleep apnea
Lammers et al.	1991	• Patients with narcolepsy with typical EDS, sleep attacks, and at least one of the accessory symptoms (cataplexy, hypnogogic hallucinations, or sleep paralysis)	• N= 28 (N=16, ritanserin; N=12, placebo) • Mean age = 43 years (range 16-67) • 11 patients used no medications, 9 used 1 drug, 7 used 2 drugs, 1 took 3 drugs • 12 used psychostimulants, 6 used antidepressants, 5 used GHB, 3 used other drugs • All patients continued to use their pretrial drugs at the same dosage
Guilleminault et al.	1986	• Patients with narcolepsy documented with PSG and MSLT for a minimum of 5 years • No sleep apnea or any other cause of daytime sleepiness	• N= 22 (M:F = 5:17) • Mean age = 53.3 years (range 33-73) • All patients complained of daytime sleepiness and cataplexy • All patients had at least 2 SOREMPs at MSLT • Patients did not take any narcolepsy-related drugs for 15 days prior to diagnostic evaluation
Schrader et al.	1986	• Patients with narcolepsy documented • All patients had EDS, sleep attacks, disturbed nocturnal sleep and unequivocal attacks of emotionally precipitated cataplexy, considered mandatory for the diagnosis of narcolepsy	• N=10 (M:F = 6:4) • Mean age = 50 years (range 36-67) • Nine patients had hypnogogic hallucinations and 7 of them also exhibited sleep paralysis. Five patients had frequent and frightening nightmares, • The average duration of narcoleptic symptoms was 28 years. • 8 patients used clomipramine before the trial with femoxetine and were satisfied with the effect on accessory symptoms. Because of side effects, however, they decided to try another drug treatment.

Reference	Year	Enrollment criteria	Baseline Pt Characteristics
Schachter and Parks	1980	• Patients with Narcolepsy	• N=18 (M:F = 11:7) • Mean age = 48.8 years (range 31-68) • The duration of cataplexy ranged from 1-52 years (mean 19 6 years). • Cataplexy untreated, was assessed as mild in five patients, moderate in six cases and severe in seven cases. • Narcolepsy was mild in two cases, moderate in eight cases and severe in the remaining eight cases. • Thirteen patients suffered from sleep paralysis and the same number had hypnapompic or hypnogogic hallucinations. Twelve patients also had disturbed night sleep. • At the start of the trial, 15 patients were taking clomipramine 25 to 100 mg daily (mean 49 mg). The remaining three patients, all with mild cataplexy, were taking mazindol 4 to 6 mg daily in two cases and on no treatment in one case. Four patients were taking clomipramine alone at a dose of 25 to 50 mg daily, five patients were taking clomipramine with mazindol 4 to 6 mg daily, five patients were taking clomipramine with dextroamphetamine 15 to 375 mg daily, and one patient was taking clomipramine with ephedrine 90 mg daily.

EDS = Excessive daytime sleepiness
GHB = Gamma hydroxy butyrate
HLA-DR2 = Broad antigen serotype associated with narcolepsy
ICSD-2 = International Classification of Sleep Disorders
M:F = Male to female ratio
MSLT = Mean Sleep Latency Test
$MSLT_{neg}$ = Patients with MSLT < 5 min
MWT = Maintenance of Wakefulness Test (measured in min)
SOREMPs = Sleep onset REM periods
SD = Standard deviation

Quality of Included Studies

The results of our assessment of the quality of the studies included in this evidence base are presented in Appendix F and summarized in Table 37.

Three of the included studies were crossover controlled trials (of "Moderate" to "High" quality), while five studies were controlled trials ranging in quality from "Low" to "High".

Table 37: Quality of Included Studies – Studies of Antidepressants

Reference	Year	Quality Scale Used	Quality Rating
Mayer et al.	2003	Quality Assessment Checklist for Controlled Trials	High
Mayer et al.	1995	Quality Assessment Checklist for Controlled Trials	High
Reinish et al.	1995	Quality Assessment Checklist for Controlled Trials	Low
Hublin et al.	1994	Quality Assessment Checklist for Crossover Controlled Trials	High
Lammers et al.	1991	Quality Assessment Checklist for Controlled Trials	High
Guilleminault et al.	1986	Quality Assessment Checklist for Controlled Trials	Low
Schrader et al.	1986	Quality Assessment Checklist for Crossover Controlled Trials	High
Schachter & Parkes	1980	Quality Assessment Checklist for Crossover Controlled Trials	Moderate

Findings

The outcomes addressed by the studies that examined the efficacy of antidepressants and the measures used to assess these outcomes are presented in Table 38.

Table 38: Outcomes Assessed and Measures Used – Studies of Antidepressants

Reference	Year	Study Design	Outcomes Assessed				
			Crash	Driving ability	Cataplexy	EDS	Cognitive and Psychomotor Performance
Efficacy Studies							
Mayer	2003	RCT	-	-	Survey for Cataplexy Symptom	Daytime Sleepiness Assessment, Sleep Latency	-
Mayer et al.	1995	RCT	-		Survey for Cataplexy Symptom	MSLT Survey for tiredness	-
Reinish et al.	1995	CT	-	-	Survey for Cataplexy Symptoms	MSLT, MWT Survey for EDS	-
Hublin et al.	1994	RCT			Survey for Cataplexy Symptoms	MSLT Survey for EDS, sleep attacks,	-
Lammers et al.	1991	RCT	-	-	Survey for Cataplexy Symptoms	MSLT Survey for EDS	-
Guilleminault et al.	1986	CT with X-over	-		Survey for Cataplexy	MSLT, MWT	WAT

Reference	Year	Study Design	Outcomes Assessed				
			Crash	Driving ability	Cataplexy	EDS	Cognitive and Psychomotor Performance
					Symptoms		
Schrader et al.	1986	RCT	-	-	Survey for Cataplexy Symptoms	MSLT, Survey for EDS	
Schachter and Parks	1980	RCT	-	-	Survey for Cataplexy Symptoms	Survey for EDS	-
TOTALS			0	0	8	8	1

CT = Controlled trial
EDS = Excessive daytime sleepiness
MSLT = Mean Sleep Latency Test
MWT = Maintenance of Wakefulness Test
RCT = Randomized controlled trial
WAT = Wilkinson Addition Test
X-over = Crossover

Direct Evidence – Impact of Antidepressants for Narcolepsy on Crash Risk

None of the included studies assessed the impact of treatment with antidepressants on crash risk.

Indirect Evidence – Impact of Antidepressants for Narcolepsy on Driving Performance (Simulated or Closed Course) Studies, Studies of Symptoms Associated with Crash Risk

All eight of the included studies assessed the efficacy of antidepressants on both symptoms of cataplexy (the primary use of these drugs with narcolepsy) and measures of daytime sleepiness. One study also assessed the efficacy of treatment on the WAT (a cognitive performance test). None of the included studies assessed the impact of treatment with antidepressants on simulated driving performance.

Impact of Antidepressants on Cataplexy Events

Table 39 shows the results of various antidepressants on cataplexy attacks. In the studies examined, cataplexy is examined as the self-reported number of attacks. Outcomes are expressed as either mean weekly number of attacks, ratios of treatment values vs. baseline, or as percent improved.

Table 39: Impact of Antidepressants on Cataplexy

Reference	Year	Study Design	Measure	Findings	Evidence that drug improves outcome?	Evidence that drug improves outcome to normal?
Mayer	2003	RCT	Number of Cataplexy Attacks	**Control**: Ratio treatment vs. baseline: 1.1 ±0.3 **Ritanserin 5 mg**: Ratio treatment vs. baseline: 1.0 ±0.5, ns **Ritanserin 10 mg**: Ratio treatment vs. baseline: 0.9 ±0.2, ns	No	No
Mayer et al.	1995	RCT	Survey of Cataplexy Symptoms	Tiredness and cataplexies were significantly reduced for the 20 mg/d **selegiline** group ($P<0.03$)	Yes At higher dose	No
Reinish et al.	1995	CT	Survey of Cataplexy Symptoms	**Selegiline (15-30 mg):** 50% reported improvement; 50% report worse or unchanged	Yes for some	No

Reference	Year	Study Design	Measure	Findings	Evidence that drug improves outcome?	Evidence that drug improves outcome to normal?
				Methylphenidate: 33% reported improvement; 67% reported worse or unchanged		
Hublin et al.	1994	RCT	Survey of Cataplexy Symptoms	Cataplexy attacks decreased in a dose-dependent manner. **Placebo**: Wkly number of attacks = 5.4 ±7.4 **Selegiline 40 mg**: Wkly number of attacks = 0.6 ±1.3 (P=0.008) **Selegiline 30 mg**: Reduced compared to placebo (P<0.01)	Yes At 30 and 40 mg	No
Lammers	1991	RCT	Survey of Cataplexy Symptoms	No statistically significant intra or inter-group differences in subjective reports of the number of cataplexy attacks with the treatment of **ritanserin**	No	No
Guilleminault et al.	1986	Non-randomized crossover	Survey of Cataplexy Symptoms	Significantly reduced with treatment of **viloxazine** when compared to baseline, placebo and post-treatment withdrawal (P<0.05)	Yes	No
Schrader et al.	1986	RCT	Survey of Cataplexy Symptoms	Nine patients recorded fewer cataplectic attacks during treatment with **femoxetine** (P<0.02) and for the severity score (P<0.05) of the attacks per 24h The median number of attacks per day was 1.89 (range: 1.00 - 5.57) during the run-in period, 1.71 (range: 0.68 - 4.68) during the placebo period and 0.55 (range: 0.10 - 3.04) during treatment.	Yes	No
Schachter and Parks	1980	RCT	Survey of Cataplexy Symptoms	**Clomipramine** 25 to 200 mg daily appeared to be more effective than **fluvoxamine** 25 to 200 mg daily in preventing both cataplexy and sleep paralysis.	Yes	No

*Primary outcome measure for study
CT = Controlled trial
NS = Not significant
RCT = Randomized Controlled Trial
UNS = Ullanlinna Narcolepsy Scale
WAT = Wilkinson Addition Test

Decreases in self-reported attacks of cataplexy were observed for some but not all of the antidepressants considered. In addition, because in no instance did attacks go down to zero, on average, it cannot be assumed that in any study, a given drug allowed patients to attain normal levels.

Dose-dependent reductions in cataplexy were reported with selegiline. However, because of newer treatments such as sodium oxybate, and because use of selegiline (a MAO-B inhibitor) is limited by potential drug interactions and diet-induced interactions, its use in treating cataplexy is not considered a first line treatment by the AASM.

Use of ritanserin in two studies showed no improvements in self-reported cataplexy attacks compared to normal.

Studies that looked at other antidepressants such as the tricyclics (clomipramine), SSRIs (fluvoxamine and femoxetine), and SNRIs (venlafaxine, and reboxetine) show variable reductions in self-reported cataplexy. As noted above, however, normal levels of no cataplexy are not attained on average for any of the drugs assessed in these studies.

Impact of Antidepressants on EDS

Table 40 shows findings from efficacy studies of various antidepressants for the treatment of EDS associated with narcolepsy. The primary outcomes assessed in these trials were self-reported sleepiness as measured by variable surveys, as well as polysomnographic sleep parameters such as MWT and MSLT. Descriptions of the sleep latency tests, along with normative values were presented above when describing the effect of modafinil (or armodafinil) on EDS. Normative values for the general surveys of sleepiness used in the present studies are not available, and it is not clear from any of the studies whether a formal standardized survey of EDS was used.

Table 40: Impact of Antidepressants on EDS

Reference	Year	Study Design	Measure	Findings	Evidence that drug improves outcome?	Evidence that drug improves outcome to normal?
Mayer	2003	RCT	Daytime sleepiness evaluation	**Control**: Ratio treatment vs. baseline: 1.0 ±0.8, ns **Rit 5 mg**: Ratio treatment vs. baseline: 1.1 ±0.4, ns **Rit 10 mg**: Ratio treatment vs. baseline: 0.9 ±0.3, ns	No	No
			Sleep Latency	**Control**: Baseline vs. 4 wk measures: – 21.2 min ±2.4 vs. 24.3 min ±4.6 **Rit 5 mg**: Baseline vs. 4 wk measures: – 21.4 min ±2.5 vs. 21.3 min ±2.8, ns **Rit 10 mg**: Baseline vs. 4 wk measures: – 27.2 min ±2.4 vs. 20.4 min ±3.7, ns	No	Not defined in terms that allow a comparison
Mayer et al.	1995	RCT	MSLT	**Sleep latency and # of REM period showed significant dose-dependent change.** Sleep latency: • 20 mg selegiline > placebo (*P*=0.008) # REM periods: • 10 mg selegiline < placebo (*P*=0.08) • 20 mg selegiline < placebo (*P*=0.0001) • 20 mg selegiline < 10 mg selegiline (*P*=0.03)	Yes At higher dose for latency	Cannot be determined from the change scores
			Survey of tiredness	Tiredness was significantly reduced for the 20 mg/d selegiline group compared to placebo (*P*<0.05)	Yes At higher dose	--

Reference	Year	Study Design	Measure	Findings	Evidence that drug improves outcome?	Evidence that drug improves outcome to normal?
Reinish et al.	1995	CT	MSLT	**Baseline MSLT:** selegiline vs. methylphenidate 2.9 ±1.5 min vs. 3.2 ±2.1 (ns) **After treatment with Selegiline (15-30 mg):** • The number of stage changes per hour significantly increased to 22.4 (±10.9 min) from 13.6 (+3.8 min) *P*<0.01. • REM latency increased from 48.7 (±42.3 min) to 138.1 (±62.8 min) *P*<0.05 • No change in sleep latency, total sleep time, sleep efficiency, the # awakenings per hour, or % of SPT in stage 1, 2, 3, 4 or REM **After treatment with Methylphenidate:** • REM latency lengthened from 52.4 (±23.7 min) to 116 (±78.3 min) • No change in sleep latency, total sleep time, sleep efficiency, the # awakenings per hour, or % of SPT in stage 1, 2, 3, 4 or REM	No	No
			MWT	**Selegiline(15-30 mg) vs. Methylphenidate Post Treatment** 9.4 (+4.8 min) vs. 18.4 (+1.9 min) *P*<0.001	No (selegiline)	No
			Survey EDS	**Selegiline (15-30 mg):** 73% reported improvement in EDS **Methylphenidate**: 75% reported improvement in EDS	Yes	Cannot be determined
Hublin et al.	1994	RCT	MSLT	The number of SOREMPs decreased in a dose-dependent manner **Median SOREMPs per wk** **Placebo**: 3.5 **Selegiline 40 mg**: 0.0 (*P*=0.0001) **Selegiline 10, 20 and 30 mg**: Reduced compared to placebo (*P*<0.01) **Median REM sleep latency (min)** **Placebo**: 3.5 min **Selegiline 40 mg**: 15 min (*P*<0.0001) **Selegiline 10, 20 and 30 mg**: Increased compared to placebo (*P*<0.01) **Mean S0 and S1 latencies (min)** **Placebo**: 1.7 min **Selegiline 40 mg**: 2.0 min (*P*=ns)	Yes SOREMPs & REM latencies No S0 & S1 latencies	No

Reference	Year	Study Design	Measure	Findings	Evidence that drug improves outcome?	Evidence that drug improves outcome to normal?
			Survey EDS	Sleepiness and daytime sleep decreased in a dose-dependent manner. **Mean # sleep episodes per wk** **Placebo**: 13.5 ±4.7 **Selegiline 40 mg**: 8.7 ±5.2 (*P*=0.001) **Selegiline 20 and 30 mg**: Reduced compared to placebo (*P*<0.05) **Mean duration of sleep episodes (Hrs per wk)** **Placebo**: 8.8 ±7.8 **Selegiline 40 mg**: 5.8 ±7.3 (*P*=0.0001) **Selegiline 10, 20 and 30 mg**: Reduced compared to placebo (*P*<0.05) **Mean # sleepiness episodes per wk** **Placebo**: 6.7 ±6.8 **Selegiline 40 mg**: 3.8 ±5.4 (*P*=0.016) **Mean # sleepiness duration per wk (Hrs per wk)** **Placebo**: 4.9 ±5.9 **Selegiline 40 mg**: 2.6 ±4.3 (*P*=0.014)	Yes (40 mg)	Cannot be determined
Lammers et al.	1991	RCT	MSLT	No significant difference between baseline or placebo vs. treatment groups	No	No
			Survey EDS	The feeling of being refreshed in the morning and subjective EDS improved with treatment but not with placebo compared to baseline (intra-treatment groups). The post-treatment inter-group comparison was also significant (*P*<0.05)	Yes	Cannot be determined
Guilleminault et al.	1986	CT with X-over	MSLT MWT	• Sleep latencies were mot significantly different for either MSLT or MWT, but percentages of REM sleep during MSLT and MWT decreased significantly with treatment (*P*<0.05) • Patients reported significant decreases in # of sleep attacks (*P*<0.05)	No sleep latencies Yes REM sleep and # sleep attacks	No
Schrader et al.	1986	RCT	MSLT	No significant difference between baseline or placebo vs. treatment groups	No	No
			Survey EDS	• EDS was not improved significantly during the **femoxetine** treatment. • Total estimated daytime sleep (8 a.m. - 8 p.m.) decreased from an average of 102 (SD ± 51) min during the placebo period to an average of 82 (SD ± 45) min during the **femoxetine** therapy, but the difference did not achieve statistical significance.	No	Cannot be determined
Schachter and Parks	1980	RCT	Survey EDS	• **Fluvoxamine** had a slight alerting effect in a minority of patients. • **Clomipramine** had no alerting effect in patients	No	Cannot be determined

CT = Controlled trial
EDS = Excessive daytime sleepiness
MSLT = Mean Sleep Latency Test
MWT = Maintenance of Wakefulness Test
RCT = Randomized controlled trial
SOREMP = Sleep onset REM period
VAS = Visual Analog Scale for Sleepiness
X-over = Crossover

The efficacy of antidepressants for symptoms of sleepiness are variable in the results of the studies considered. For example, in most cases, sleep latencies on the MSLT and/or the MWT were not increased following drug treatment. Patients treated with selegiline (typically at the higher doses) demonstrated moderate improvements in symptoms of sleepiness, but the results among the three studies that examined efficacy of selegiline were mixed.

Impact of Antidepressants on Cognitive and Psychomotor Function

Table 41 presents the results of one study that assessed the impact of antidepressants on cognitive function (i.e., the Wilkinson Addition Test).

Table 41: Impact of Antidepressants on Cognitive and Psychomotor Function

Reference	Year	Study Design	Measure	Findings	Evidence that drug improves outcome	Evidence that drug improves outcome to normal
Guilleminault et al.	1986	CT with X-over	WAT	Number of problems solved did not change between placebo, baseline and treatment	No	--

CT = Controlled trial
WAT = Wilkinson Addition Test
X-over = Crossover

As shown in the table above, treatment with viloxazine had no impact of WAT scores.

Summary of Findings

Direct Evidence – Crash Studies:

- **Evidence-based conclusions pertaining to the impact of treatment with antidepressants on crash risk among individuals with narcolepsy cannot be drawn at this time.**

No studies that directly examined the impact of treatment with antidepressants for narcolepsy on crash risk were identified by our searches.

Indirect Evidence: Driving Performance (Simulated or Closed Course) Studies, Studies of Symptoms Associated with Crash Risk:

- **Evidence-based conclusions pertaining to the impact of treatment with antidepressants on driving performance among individuals with narcolepsy cannot be drawn at this time.**

No studies that directly examined the impact of with antidepressants for narcolepsy on driving performance were identified by our searches.

- **Evidence-based conclusions pertaining to the impact of treatment with antidepressants on cataplexy events among individuals with narcolepsy cannot be drawn at this time.**

Eight studies examined the impact of antidepressants on the frequency of cataplexy symptoms. Decreases in self-reported attacks of cataplexy were observed for some but not all of the antidepressants considered. For instance three studies (Quality Rating: two "high," one "Low") found dose-dependent

reductions in cataplexy with the use of selegiline while two other studies (Quality Rating: "High") using ritanserin showed no improvements in symptoms of cataplexy. Three other studies (Quality Rating: one "Low," one "Moderate," one "High") looked at the impact of tricyclic antidepressants (clomipramine), SSRIs (femoxetine), or SNRIs (viloxazine) on self-reported cataplexy. Each of these studies demonstrated significant improvements in reports of cataplexy for patients under the respective treatments. However, when improvements were demonstrated, they did not reach normal levels.

- **Evidence-based conclusions pertaining to the impact of treatment with antidepressants on measures of daytime sleepiness among individuals with narcolepsy cannot be drawn at this time.**

Eight studies examined the impact of antidepressants on measures of daytime sleepiness associated with narcolepsy. Three studies examined the use of selegiline (Quality Rating: two "high," one "Low") on measures of daytime sleepiness. Selegiline produced dose-dependent improvements in self-reported sleepiness (measured by survey). Similarly, selegiline produced dose-dependent improvements sleep latencies on the MWT and/or MSLT reaching significance only at the highest doses (20 mg and 40 mg). Two high quality studies of the impact of ritanserin showed mixed results on improving subjective reports of daytime sleepiness, and demonstrated no improvements on measures of sleep latencies. In three other studies (Quality Rating: one "Low," one "Moderate," one "High") the antidepressants assessed (i.e., clomipramine, femoxetine, and viloxazine) demonstrated little or no improvement for any measures of daytime sleepiness. When improvements were demonstrated for any of the antidepressants assessed, they did not reach normal levels.

- **Evidence-based conclusions pertaining to the impact of treatment with antidepressants on cognitive and psychomotor function among individuals with narcolepsy cannot be drawn at this time.**

A single study (Quality Rating: "Low") assessed a measure of cognitive function (WAT) and found no significant improvements.

Key Question 2D: What is the Impact of Treatment with Amphetamine, Methylphenidate, and/or Other Stimulants for Narcolepsy on Driver Safety?

Amphetamine, methamphetamine, dextroamphetamine, methylphenidate, and other related drugs were previously the mainstays for treatment of sleepiness associated with narcolepsy. Availability of modafinil and armodafinil has relegated the use of these drugs to second line treatments in cases where modafinil or armodafinil are unsuccessful, largely because of the risks associated with these drugs.

Study Design Characteristics

Design details of the three included studies that examined the impact of treatment with amphetamine and/or methylphenidate on outcomes relevant to driver safety are presented in Table 42.

Table 42: Study Design Details – Studies of Amphetamine and Methylphenidate

Reference	Year	Study design	No. of centers	N =	Cross-over?	Blinding	Study Duration	Control	Treatment
Mitler et al.	1993	RCT	1	16	Yes	Double	6 wks 2wk washout 4 wk treatment (4 days on followed by 3 days off; 4 cycles)	**Normal matched controls (N=8)** Treatment 1 Methamphetamine 0 mg/day (morning) (4 days on - 3 days off) Treatment 2 Methamphetamine 5 mg/day (morning) (4 days on - 3 days off) Treatment 3 Methamphetamine 10 mg/day (morning) (4 days on - 3 days off)	**Narcolepsy Patients (N=8)** Treatment 1 Methamphetamine 0 mg/d (morning) (4 days on - 3 days off) Treatment 2 Methamphetamine 20 mg/d (morning) (4 days on - 3 days off) Treatment 3 Methamphetamine 40-60 mg/d (morning) (4 days on - 3 days off)
Mitler et al.	1986	RCT	1	26	Yes	Double	4 wks 1 wk baseline (no meds) 1 wk low dose 1 wk intermediate dose 1 wk high dose (order of dose level was randomized)	**Normal matched controls** Placebo Capsules 3x/day (controls were told that the drug was either low, intermediate, or high dose of stimulant drug)	**Narcolepsy Patients** Treatment 1 Methylphenidate, 10, 30, and 60 mg/d (3x/day, 1/3rd of the assigned dose) Treatment 2 Pemoline, 18.75, 56.25, and 112.5 mg/d (3x/day, 1/3rd of the assigned dose) Treatment 3 Protriptyline 10, 30, and 60 mg/d (3x/day, 1/3rd of the assigned dose)
Shindler et al.	1985	RCT	1	20	Yes	Double	**Phase 1** 12 wks 3, 4 wk cross-over treatment periods **Phase 2** 8 wks 2, 4 wk cross-over treatment periods	Placebo A placebo matched each of the treatment drugs. During both phase 1 and phase 2, patients only ever received 1 active drug at any given time, along with placebo version of the remaining drugs. Within a phase, the order of the active drugs given to each patient was randomized and double blinded. Phase 1 was always followed by phase 2	**Phase 1** Treatments 1-3 (low dose) 1. Dexamphetamine sulphate as Dexedrine tablets (5 mg twice daily, morning and noon) 2. Dexamphetamine sulphate as Dexedrine capsules (10 mg single dose, morning) 3. Mazindol (Teronac) (2 mg twice daily, morning and noon) **Phase 2** Treatments 1-2 (high dose) 1. Dexamphetamine sulphate as Dexedrine tablets (10 mg three times daily, morning, noon, and afternoon) 2. Fencamfacin hydrochloride (20 mg three times daily, morning, noon, and afternoon)

RCT = Randomized controlled trial

Characteristics of Enrollees

The purpose of this subsection is to provide details about the characteristics of patients included in the amphetamine studies and the extent to which these individuals are: 1) generalizable to individuals with narcolepsy in the general population; and 2) are similar to CMV drivers in the United States. Enrollment criteria and baseline characteristics of the patients included in each of these studies are presented in Table 43.

Of the three studies included, 34.6% to 45.0 percent consisted of males. The mean age for treatment and comparison groups in this study ranged from 39.2 to 54.5 years, and included patients whose age fell between 28 and 65 years. For two studies (Mitler et al., 1993 and Mitler et al., 1986), the age range was not reported.

Narcolepsy subjects were recruited from sleep disorder clinics and therefore, are representative of the narcolepsy population currently receiving treatment. Diagnoses of narcolepsy, in these studies, were primarily based on accepted medical standards (e.g., ICDS diagnostic criteria).

Most studies excluded subjects (both cases and controls) with any evidence of a medical or psychiatric disorder that might account for or contribute to their condition. Sleep apnea and any sleep disorder other than narcolepsy were also typically included as exclusion criteria.

The generalizability of the findings of the included studies to CMV drivers is unclear as none of the included studies examined narcolepsy specifically among CMV drivers. The mean age of participants included in these studies (typically in the 40's) is relatively comparable to the average age of CMV drivers (43 years); however, females were largely over-represented in these studies compared to the CMV driver population.

Table 43: Characteristics of Enrollees – Studies of Amphetamine and/or Methylphenidate

Reference	Year	Enrollment criteria	Baseline Pt Characteristics
Efficacy Studies			
Mitler et al.	1993	• Criteria for narcoleptics were: a) clinical history of excessive somnolence; b) mean sleep latency on a diagnostic four-nap MSLT of <5 minutes; c) history of hypnagogic hallucinations and/or cataplexy, but not severe enough to require treatment during the study; d) absence of other significant sleep pathology, as determined by diagnostic nocturnal polysomnography; e) two or more transitions to REM sleep on MSLT; and f) willingness to take a stimulant drug during testing protocols. • Both narcoleptics and subject controls underwent diagnostic criteria and polysomnographic evaluation, which included measures of respiration and limb movement, prior to admission into the protocol. • Polysomnographic recordings were reviewed to ensure that no sleep disorders (other than narcolepsy) were present in the narcoleptic or control groups.	• Eight pairs, each consisting of a narcoleptic patient and a healthy control subject • For every narcoleptic recruited from the Sleep Disorders Clinic population of >200, a control subject (recruited by bulletin boards and/or word of mouth) was matched to a narcoleptic on the basis of age, sex, education, and work history. • Narcoleptic sample consisted of 3 males and 5 females, mean age 42.0 years; healthy control sample mean age was 43.1 years. • All narcoleptics presented a clear history of cataplexy, but none was judge to be at significant risk by being without anticataplectic medication for the duration of the study. • All subjects carried the HLA DRw15 antigen, except for one narcoleptic who carried DR4. • Average sleep latency for narcoleptics was 1.93 (±0.89 minutes). • Average number of REM periods was 2.9 (+1.2).
Mitler et al.	1986	• Narcoleptic patients must have been free from significant medical illness other than narcolepsy and the following: a) history of excessive somnolence; b) at least one of the REM sleep-related symptoms of sleep paralysis, hypnagogic hallucinations, and cataplexy; c) nocturnal polysomnography ruling out sleep apnea syndrome; and d) two or more transitions to REM sleep on MSLT. • Control subjects must have been physically healthy and free of sleep disorder and psychiatric disorder as well as willing to take a stimulant drug during testing protocols.	**Methylphenidate (Ritalin)** • Six narcoleptic patients (M:F = 1:5) • Mean age 54.5 (± 11.7) **Pemoline (Cylert)** • Seven narcoleptic patients (M:F = 2:5) • Mean age 43.0 (± 7.1) **Protriptyline (Vivactil)** • Four narcoleptic patients (M:F = 2:2) • Mean age 42.5 (± 16.9) **Placebo (Control group)** • Nine healthy subjects (M:F = 4:5) • Mean age 39.2 (± 8.4)
Shindler et al.	1985	• All had narcolepsy. • No patient had cardiovascular, respiratory, or hepatic impairment.	• 20 patients (M:F = 9:11), age 28-65 (mean age: 49), attending King's College Hospital sleep disorders clinic for narcolepsy • Duration of narcolepsy 7-45 years of age (mean age: 25) • 12 had cataplexy • 8 had sleep paralysis • Duration of cataplexy or sleep paralysis 5-41 years (mean 21) • Polysomnographic recordings were reviewed to ensure

HLA DRw 15= Antigen associated to narcolepsy
M:F = Male to female ratio
MSLT = Mean Sleep Latency Test
REM = Rapid eye movement

Quality of Included Studies

The results of our assessment of the quality of the studies included in this evidence base are presented in Appendix F and summarized in Table 44. These studies ranged from "Low" to "Moderate".

Table 44: Quality of the Included Studies - Amphetamine and/or Methylphenidate

Reference	Year	Quality Scale Used	Quality Rating
Mitler et al.	1993	Quality Assessment Checklist for Controlled Trials	Moderate
Mitler et al.	1986	Quality Assessment Checklist for Crossover Controlled Trials	Low
Schindler et al.	1986	Quality Assessment Checklist for Crossover Controlled Trials	Low

Findings

The outcomes addressed by the studies that examined the efficacy of amphetamine, methylphenidate, and/or other stimulants for the treatment of narcolepsy, and the measures used to assess these outcomes are presented in Table 45.

Table 45: Outcomes Assessed and Measures Used – Studies of Amphetamine, Methylphenidate, and/or Other Stimulants

Reference	Year	Study Design	Outcomes Assessed				
			Crash	Driving ability	Cataplexy	EDS	Cognitive and Psychomotor Performance
Mitler et al.	1993	RCT	-	Computer-based Steer Clear driving test	-	MSLT*	
Mitler et al.	1986	RCT	-	-	-	MWT*	WAT*, DSS*
Shindler	1985	RCT	-	-	Number of Cataplexy Attacks	Attacks of Narcolepsy*, Drowsiness Rating scale*	-
TOTALS			0	1	1	3	1

*Primary outcome measure for study
DSS = Digit Symbol Substitution
EDS = Excessive daytime sleepiness
MSLT = Mean Sleep Latency Test
MWT = Maintenance of Wakefulness Test
RCT = Randomized controlled trial
WAT = Wilkinson Addition Test

Direct Evidence – Impact of Amphetamines, Methylphenidate, and/or other Stimulants for Narcolepsy on Crash Risk

None of the included studies assessed the impact of treatment with amphetamines, methylphenidate or other stimulants for narcolepsy on crash risk.

Indirect Evidence – Impact of Amphetamines, Methylphenidate, and/or other Stimulants for Narcolepsy on Driving Performance (Simulated or Closed Course) Studies, Studies of Symptoms Associated with Crash Risk

All three studies assessed the use of these medications on daytime sleepiness, and one of each of the studies examined the impact of treatment on driving ability, self-reported symptoms of cataplexy, and cognitive and psychomotor performance.

Impact of Amphetamine and/or Methylphenidate on Driving Performance

Table 46 presents the results of one study that assessed the impact of variable doses of methamphetamine on simulated driving performance using the Steer Clear driving simulator task.

Table 46: Impact of Amphetamine and/or Methylphenidate on Driving Performance

Reference	Year	Study Design	Measure	Findings	Evidence that drug improves outcome?	Evidence that drug improves outcome to normal?
Mitler	1993	RCT	Steer Clear driving simulator: Percentage of objects hit	**Narcoleptics:** Baseline 2.96 (±2.23) (*P*<0.04) Placebo: 2.53 (±2.29) (*P*<0.04) Methamphetamine low dose (20mg): 0.47 (±0.30) (*P*<0.02) Methamphetamine high dose (40-60mg): 0.32 (±0.29) (*P*<0.02) **Control subjects:** Baseline 0.83 (±1.02) (*P*<0.04) Placebo: 0.22 (±0.26) (*P*<0.04) Methamphetamine low dose (5mg): 0.14 (±0.19) (*P*<0.02) Methamphetamine high dose (10mg): 0.16 (±0.19) (*P*<0.02)	Yes	No

RCT = Randomized controlled trial

As described above (Table 46), the percent of objects hit on the Steer Clear driving simulator test decreased significantly in a dose-dependent manner following treatment with methamphetamine for both patients with narcolepsy and normal controls. Patients with narcolepsy who received the higher dose of methamphetamine (60 mg) did not hit more objects than controls who received placebo. They did, however, hit more objects than control subjects receiving 10 mg of methamphetamine. While the evidence suggests that methamphetamine improves simulated driving performance, the number of narcolepsy patients included in this study was quite small.

Impact of Amphetamines and/or Methylphenidate on EDS

Table 47 presents the results of all three studies included the evidence base for amphetamines, methylphenidate, or other related drugs. The primary outcomes assessed in these trials were self-reported sleepiness as measured either by the ESS (Mitler et al., 1993) or by survey (Schindler, 1985), as well as polysomnographic sleep parameters such as MWT (Mitler et al., 1986) and MSLT (Mitler et al., 1993). Descriptions of the sleep latency tests, along with normative values were presented above when describing the effect of modafinil (or armodafinil) on EDS. Normative values for the general survey of sleepiness utilized by Schindler (1985), are not available.

Table 47: Impact of Amphetamine and/or Methylphenidate on EDS

Reference	Year	Study Design	Measure	Findings	Evidence that drug(s) improves outcome?	Evidence that drug improves outcome to normal?
Mitler et al.	1993	RCT	MSLT	The effects of methamphetamine on nocturnal sleep were generally dose-dependent and appeared to be concentrated on parameters reflecting sleep continuity and REM sleep. Sleep efficacy was significantly improved in both groups at the high dose. No systematic effects were found for order of laboratory testing in either group. Narcolepsy patients: • Baseline 4.53 (±3.41) (*P*<0.03) • Placebo: 4.29 (±3.12) (*P*<0.03) • Methamphetamine low dose (20mg): 7.75 (±4.82) (*P*<0.0005) • Methamphetamine high dose (40-60mg): 9.27 (±4.65) (*P*<0.0005) Control subjects: • Baseline 12.25 (±4.22) (*P*<0.03) • Placebo: 10.35 (±5.26) (*P*<0.03) • Methamphetamine low dose (5mg): 14.64 (±3.99) (*P*<0.0005) • Methamphetamine high dose (10mg): 17.11 (±3.79) (*P*<0.0005)	Yes Dose-dependent	No
Mitler et al.#	1986	RCT	MWT	Control: Baseline 18.9 (±2) (*P*<0.05) Placebo Dose 1 (low): 19.2 (±2) (*P*<0.05) Placebo Dose 2 (intermediate): 18.0 (±4) (*P*<0.05) Placebo Dose 3 (high): 17.6 (±4) (*P*<0.05) Methylphenidate: Baseline 12.8 (±7) (*P*<0.05) Dose 1 (10 mg): 15.2 (+6) (*P*<0.05) Dose 2 (30 mg): 15.4 (+7) (*P*<0.05) Dose 3 (60 mg): 18.0 (+4) (*P*<0.025) Protriptyline: Baseline 10.0 (±5) (*P*<0.05) Dose 1 (10 mg): 10.0 (±7) (*P*<0.05) Dose 2 (30 mg): 10.6 (±7) (*P*<0.05) Dose 3 (60 mg): 11.6 (±6) (*P*<0.05)	Yes	Yes (Methamphetamine on high dosage approached normal levels)
Shindler	1985	RCT	Number of Narcolepsy Attacks	No Treatment: 4.4 (0.6) Dexamphetamine tablet: (low): 2.7 (0.7) Dex spansule: 2.4 (0.7) (*P*<0.05) Mazindol: 2.1 (0.5) Dexamphetamine tablet: (high): 2.2 (0.3) (*P*<0.01) Fencamfamin: 2.8 (0.5) (*P*<0.05)	Yes	No
			Drowsy Rating (0-100 scale)	No Treatment: 24.2 (4.8) Dexamphetamine tablet: (low): 34.9 (5.9) Dexamphetamine spansule: 40.4 (6.0) (*P*<0.05) Mazindol: 47.3 (5.1) (*P*<0.001) Dexamphetamine tablet: (high): 56.8 (4.5) (*P*<0.001) Fencamfamin: 57.3 (4.7) (*P*<0.001)	Yes	No

The results related to Pemoline use are not described because this drug is no longer available for use in the United States. The FDA withdrew this drug from the market in 2005 due to rare but potentially lethal liver toxicity associated with use of this drug.

*Primary outcome measure for study
ESS = Epworth Sleepiness Scale
MSLT = Mean Sleep Latency Test
MWT = Maintenance of Wakefulness Test
RCT = Randomized controlled trial
REM = Rapid eye movement

As shown in the table above (Table 47), in all three of the studies examined, subjects treated with methamphetamine, methylphenidate, or dexamphetamine showed evidence of improvement on all measures of daytime sleepiness (e.g., ESS, and latencies for the MWT and MSLT) compared either with placebo treated groups, or baseline values. In addition, the responses were found to be dose-dependent. Mitler et al., (1993) found that daytime sleepiness measured with the ESS was significantly reduced in both patients with narcolepsy and normal controls when treated with the higher dose of methamphetamine. Latencies on the MWT (Mitler et al., 1986) were also significantly increased in patients treated with the higher dose of methylphenidate, approaching normal levels. There was also a clear dose-dependent response observed by Schindler (1985) on subjective assessments of sleepiness and the number of daytime narcolepsy attacks with dexamphetamine. In all cases, however, the number of patients included in the respective "Moderate" to "Low" quality studies was small, thus limiting the conclusions that can be drawn.

Impact of Amphetamine, Methylphenidate, and/or other Stimulants on Cataplexy

Table 48 presents the result of one study that assessed the impact of dexamphetamine and mazindol on the number of cataplexy attacks.

Table 48: Impact of Amphetamine and/or other Stimulants on Cataplexy

Reference	Year	Study Design	Measure	Findings	Evidence that drug improves outcome?	Evidence that drug improves outcome to normal?
Shindler	1985	RCT	Number of Cataplexy Attacks	No Treatment: 2.1 (SEM=0.6)	No	No
				Dexamphetamine tablet: (low): 2.0 (SEM=0.6)	No	
				Dexamphetamine spansule: 2.1 (SEM=0.8)	No	
				Mazindol: 1.2 (SEM=0.4)	No	
				Dexamphetamine tablet (high): 1.4 (SEM=0.9)	No	
				Fencamfamin: 2.5 (SEM=1.0)	No	

RCT = Randomized controlled trial
SEM = Standard error of mean

As shown above (Table 48) none of the drugs assessed significantly reduced numbers of cataplexy attacks compared to baseline.

Impact of Amphetamine and/or Methylphenidate on Cognitive and Psychomotor Function

Table 41 presents the result of one, low quality study that assessed the impact of methylphenidate or protriptyline on cognitive function (i.e., the WAT and DSS tests).

Table 49: Impact of Amphetamine, Methylphenidate, and/or other Stimulants on Cognitive and Psychomotor Function

Reference	Year	Study Design	Measure	Findings	Evidence that drug improves outcome	Evidence that drug improves outcome to normal?
Mitler et al.[#]	1986	RCT	WAT	**Control:** Baseline 100.0 (±24) (*P*<0.05) Dose 1 (low): 118.4 (±32) (*P*<0.005) Dose 2 (intermediate): 123.4 (±39) (*P*<0.005) Dose 3 (high): 123.4 (±38) (*P*<0.005)	Yes	No
				Methylphenidate: Baseline 71.6 (±38) (*P*<0.05) Dose 1 (low): 71.6 (±33) (*P*<0.05) Dose 2 (intermediate): 71.8 (±31) (*P*<0.05) Dose 3 (high): 84.5 (±40) (*P*<0.005)		
				Protriptyline: Baseline 56.3 (±16) (*P*<0.05) Dose 1 (low): 68.1 (±23) (*P*<0.05) Dose 2 (intermediate): 72.6 (±23) (*P*<0.05) Dose 3 (high): 64.2 (±25) (*P*<0.05)		
			DSS	**Control:** Baseline 731.3 (±114) (*P*<0.05) Dose 1 (low): 811.9 (±159) (*P*<0.005) Dose 2 (intermediate): 843.2 (±160) (*P*<0.005) Dose 3 (high): 849.7 (±155) (*P*<0.005)	Yes	No
				Methylphenidate: Baseline 404.6 (±183) (*P*<0.05) Dose 1 (low): 476.2 (±164) (*P*<0.025) Dose 2 (intermediate): 534.4 (±207) (*P*<0.005) Dose 3 (high): 557.0 (±101) (*P*<0.005)		
				Protriptyline: Baseline 404.3 (±151) (*P*<0.05) Dose 1 (low): 501.8 (±191) (*P*<0.05) Dose 2 (intermediate): 504.8 (±212) (*P*<0.05) Dose 3 (high): 422.6 (±226) (*P*<0.05)		

# The results related to Pemoline use are not described because this drug is no longer available for use in the United States. The FDA withdrew this drug from the market in 2005 due to rare but potentially lethal liver toxicity associated with use of this drug.
DSS = Digit Symbol Substitution
RCT = Randomized controlled trial
WAT = Wilkinson Addition Test

As shown above (Table 49), treatment with methylphenidate resulted in dose-dependent improvements on both the WAT and the DSS tests. Treatment with protriptyline (a tricyclic antidepressant) also resulted in significant improvements compared to baseline values. However, the responses were not dose-dependent. Relative to placebo treated normal control subject, however, neither group ever achieved normal levels, even at the highest doses of the respective drugs.

Summary of Findings

Direct Evidence: Crash Studies:

- **Evidence-based conclusions pertaining to the impact of treatment with amphetamines, methylphenidate, or other related drugs on crash risk among individuals with narcolepsy cannot be drawn at this time.**

No studies that directly examined the impact of treatment with amphetamines, methylphenidate, or other related drugs for narcolepsy on crash risk were identified by our searches.

Indirect Evidence: Driving Performance (Simulated or Closed Course) Studies, Studies of Symptoms Associated with Crash Risk:

- **Evidence-based conclusions pertaining to the impact of treatment with amphetamines, methylphenidate, or other related stimulant drugs on driving performance among individuals with narcolepsy cannot be drawn at this time.**

One study (Quality Rating: "Moderate") assessed simulated driving performance of patients with narcolepsy treated with variable doses of methamphetamine. The percent of objects hit on the Steer Clear driving simulator test decreased significantly in a dose-dependent manner following treatment with methamphetamine. While the evidence suggests that methamphetamine improves simulated driving performance, the number of narcolepsy patients included in this study was quite small (n=8). Additional evidence that replicates these findings in a larger number of individuals with narcolepsy is needed to make an evidence-based conclusion.

- **Currently available evidence suggests that amphetamines and/or methylphenidate are effective in improving symptoms of EDS in individuals with narcolepsy. However, these improvements do not result in levels of daytime sleepiness that can be considered to be normal in the vast majority of individuals (Strength of Evidence: Low to Moderate).**

Three studies (Quality Rating: one "Moderate," two "Low") examined the efficacy of amphetamines and/or methylphenidate in treating EDS. All three studies provided evidence of improvement on all measures of daytime sleepiness (e.g., ESS, and latencies for the MWT and MSLT) compared either with placebo treated groups, or baseline values. In each case the effects were dose-dependent, reaching normal levels at the highest doses.

- **Evidence-based conclusions pertaining to the impact of treatment with amphetamines, methylphenidate, or other related stimulant drugs on cataplexy events among individuals with narcolepsy cannot be drawn at this time.**

A single study (Quality Rating: "Low") assessed the impact of dextroamphetamine, mazindol, and fencamfamin on self-reported attacks of cataplexy. No improvements were demonstrated for any of these drugs on self-reported cataplexy attacks.

- **Evidence-based conclusions pertaining to the impact of treatment with amphetamines, methylphenidate, or other related stimulant drugs on cognitive and psychomotor function among individuals with narcolepsy cannot be drawn at this time.**

A single study (Quality Rating: "Low") assessed this outcome measure. Treatment of narcolepsy patients with methylphenidate resulted in dose-dependent improvements on both the Wilkinson Addition Test (WAT) and the Digit Symbol Substitution (DSS) tests. Relative to normal control subjects, however, narcolepsy patients did not achieve normal levels, even at the highest doses of methylphenidate. The number of subjects included in this study was very small. Additional evidence that replicates these findings in a larger number of individuals with narcolepsy is needed to make an evidence-based conclusion.

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Appendix A: Second Edition of the International Classification of Sleep Disorders (ICSD-2)

Diagnostic classification of sleep disorders is important because it standardizes definitions, improves awareness of the conditions, promotes a broad differential diagnosis, and facilitates a systematic diagnostic approach.

The ICSD-2 was created at the same time of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) to permit greater concordance between the systems. The ICD-9, based on the World Health Organization's Ninth Revision, International Classification of Diseases (ICD-9), is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States. The ICD-9 is used to code and classify mortality data from death certificates. The ICD-9 consists of:

- A tabular list containing a numerical list of the disease code numbers in tabular form;
- An alphabetical index to the disease entries; and
- A classification system for surgical, diagnostic, and therapeutic procedures (alphabetic index and tabular list).

The ICSD-2's eight major classifications are listed below. Table A- 1 outlines the general criteria and prevalence of conditions contained in each of the eight primary sleep disorder classifications. This is followed by a more detailed discussion of sleep disorders contained in the sleep class Hypersomnias of Central Origin Not Due to a Circadian Rhythm Sleep Disorder, Sleep Related Breathing Disorder, or Other Cause of Disturbed Nocturnal Sleep, under which narcolepsy (with and without cataplexy) is classified. A more detailed discussion of each of the other classes of sleep conditions is contained in the FMCSA commissioned report on titled Daytime Sleepiness and Commercial Driver Safety (2009).

I. Insomnia

Prevalent in about 30 percent of the population, insomnia is the most common complaint of all sleep disorders. It is characterized by difficulty in initiating or maintaining sleep, waking up too early, and non-restorative or poor quality sleep. It can be caused by a variety of biological, psychological and social factors and is listed as a symptom in most sleep disorders.

- **The ICSD-2 lists 12 types of insomnias.**

II. Sleep Related Breathing Disorders

The term breathing-related sleep disorder refers to a spectrum of breathing anomalies ranging from chronic or habitual snoring to upper airway resistance syndrome to obstructive sleep apnea, or, in other cases, sleep-related hypoventilation/hypoxemic syndromes. According to estimates, at least 2 to 4 percent of the adult population experience sleep-related breathing disorders (Kushida et al., 2006).

- **The ICSD-2 identifies 11 types of sleep-related breathing disorders.**

III. Hypersomnias of Central Origin Not Due to a Circadian Rhythm Sleep Disorder, Sleep Related Breathing Disorder, or Other Cause of Disturbed Nocturnal Sleep

Home of the three narcolepsy diagnoses, the primary complaint for people with sleep disorders within this classification is daytime sleepiness in which the cause of the primary symptom is not disturbed nocturnal sleep or misaligned circadian rhythms. Estimated to afflict about 9 percent of the adult population (Hublin et al., 1996), hypersomnia is considered to be a less common sleep disorder than insomnia and is most likely to first occur in people during adolescence and young adulthood.

- **The ICSD-2 identifies 15 types of hypersomnia.**

IV. Circadian Rhythm Sleep Disorders

Circadian rhythm sleep disorders – for which the prevalence in the U.S. population is unknown – involve a problem in the timing of when a person sleeps and is awake. The human body has a master circadian clock in a control center of the brain known as the *suprachiasmatic nucleus* (SCN). This internal clock regulates the timing of such body rhythms as temperature and hormone levels. The primary circadian rhythm that this body clock controls is the sleep-wake cycle. The circadian clock functions in a cycle that lasts a little longer than 24 hours. Each circadian rhythm sleep disorder involves one of these two problems:

- Difficulty in initiating sleep
- Struggling to maintain sleep, waking up frequently during the night
- Waking up too early and unable to go back to sleep
- Sleep is non-restorative or of poor quality.

- **The ICSD-2 identifies 10 types of circadian rhythm disorders.**

V. Parasomnias

Parasomnias are undesirable physical events or experiences that occur during entry into deep sleep, within sleep, or during arousals from sleep. Parasomnias, which affect about 10 percent of Americans, encompass abnormal sleep-related movements, behaviors, emotions, perceptions, dream and autonomic nervous system functioning. Parasomnias are clinical disorders because of the resulting injuries, sleep disruption, adverse health effects, and untoward psychosocial effects.

- **The ICSD-2 identifies 11 types of parasomnias.**

IV. Sleep Related Movement Disorders

Restless Leg Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD) are the most common of these disorders that are sleep-related movements, considered abnormal. Either a nocturnal sleep disturbance or a complaint of excessive daytime sleepiness or fatigue has to be present. With the exception of movements due to RLS, sleep-related movement disorders are relatively simple and usually stereotyped. Body movements that disrupt sleep are also seen in other sleep disorder categories (e.g. some parasomnias, sleep-related epilepsy, etc). However, these movements are more complex in nature, and they are classified separately.

- **The ICSD-2 identifies 8 types of sleep-related movement disorders.**

VII. Isolated Symptoms, Apparently Normal Variants and Unresolved Issues

Restless Leg Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD) are the most common of these disorders that are sleep-related movements, considered abnormal. Either a nocturnal sleep disturbance or a complaint of EDS or fatigue has to be present. With the exception of movements due to RLS, sleep-related movement disorders are relatively simple and usually stereotyped. Body movements that disrupt sleep are also seen in other sleep disorder categories (e.g. some parasomnias, sleep-related epilepsy, etc). However, these movements are more complex in nature, and they are classified separately.

- **The ICSD-2 identifies 9 types of isolated symptoms.**

VIII. Other Sleep Disorders

A sleep disorder is temporarily classified here if it cannot be placed elsewhere in the ICSD-2, and the expectation is that a final diagnosis will have a physiological or medical basis. This diagnosis is also used as a permanent classification for sleep disorders that cannot be placed anywhere else in ICSD-2, but are believed to be due to physiological or medical factors. This is also a default category in which to place sleep disorders not classifiable elsewhere, where there is no evidence whether the sleep disorder has a medical, or a psychiatric etiology.

- **The ICSD-2 identifies 3 types of other sleep disorders.**

Table A- 1: General Criteria and Prevalence of Major Sleep Disorder Classifications

Classification	General criteria or features	Prevalence

Insomnia	• Difficulty of initiating or maintaining sleep, waking up too early or sleep that is non-restorative or poor in quality.
	• The sleep problem occurs despite adequate opportunity and circumstances for sleep.
	• At least one of the following daytime problems is reported because of sleep difficulty:
	  ○ Fatigue
	  ○ Attention, concentration or memory
	  ○ Social or vocal dysfunction
	  ○ Mood disturbance or irritability
	  ○ Sleepiness
	  ○ Motivation, energy or initiative reduction
	  ○ Tension headaches, or gastrointestinal symptoms
	  ○ Concerns or worries about sleep
		• A general consensus has developed from population-based studies that approx 30% of a variety of adult samples drawn from different countries report one or more of the symptoms of insomnia. – **Roth (2007)**
		• 60 million or 69% of people who see primary care physicians (Estimate considered on lower end of true scale). – **Katz & McHorney (2002) and Bixler et al. (2002)**
		• About one-third of the adult American population is affected by insomnia. – **Ancoli-Israel & Roth (1999) and Kuppermann et al. (1995)**

Sleep Related Breathing Disorders (SRBD)	This disorder group is characterized by disordered respiration during sleep. Central Sleep Apnea syndromes include those in which respiratory effort is diminished or absent in an intermittent or cyclic fashion due to central nervous system or cardiac dysfunction. The obstructive sleep apnea syndromes include those in which there is an obstruction in the airway resulting in continued breathing effort but inadequate ventilation. Adult and pediatric patients are identified separately because the disorders have different methods of diagnosis and treatment. SRBD constitute a subset of the broad group of sleep disorders that include many other disorders, such as insomnia (difficulty sleeping), hypersomnias (inappropriately falling asleep, for example, narcolepsy), parasomnias (activities during sleep, for example, sleepwalking and sleep terrors), and Sleep Related Movement Disorders (for example, restless leg syndrome). Snoring and sleep apnea are the most common SRBD.	• SRBD prevalence of at least 2-5% of U.S. general population. – **Carley & Radulovaki (2003)** • Approx 1 in 22 or 4.41% or 12 million people in U.S. suffer from obstructive sleep apnea (OSA), the most diagnosed SRBD. – **Wrong Diagnosis (2009b)** • Approx 1 in 27 or 3.68% or 10 million people in U.S. have OSA but have not been diagnosed. – **Wrong Diagnosis (2009a)**
Hypersomnias of Central Origin Not Due to a Circadian Rhythm Sleep Disorder, Sleep Related Breathing Disorder, or Other Cause of Disturbed Nocturnal Sleep	This section includes disorders in which the primary complaint is daytime sleepiness and in which the cause of the primary symptom is not disturbed nocturnal sleep or misaligned circadian rhythm. In all cases in which a diagnosis of hypersomnia is to be made, a review of psychiatric history and drug and medication use and an assessment of other sleep and medical disorders should be performed.	• Estimated to affect about one in every 2,000 Americans. – **National Institute of Neurological Disorders and Stroke (2009)** • Approx 1 in 1,359 Americans, or 0.07% of the population; about 200,000 people. – **Wrong Diagnosis (2009b)** • Undiagnosed prevalence rate: approx 1 in 1,813 Americans, or 0.06% of population; 150,000 people. – **Wrong Diagnosis (2009b)**

Circadian Rhythm Sleep Disorders	• There is persistent or recurrent pattern of sleep disturbance due primarily to one of the following;
	  ○ Alterations of the circadian timekeeping system
	  ○ Misalignment between the endogenous circadian rhythm and exogenous factors that affect the timing or duration of sleep
	• The circadian-related sleep disruption leads to insomnia, EDS, or both.
	• The sleep disturbance is associated with impairment of social, occupational, or other areas of functioning.
		• The prevalence of circadian rhythm sleep disorders in the general population is unknown. – **AASM (2008a)**
		• Approximately 7-10% of patients who complain of insomnia are diagnosed with a circadian rhythm disorder. – **Cataletto and Hertz (2008)**
		• The exact incidence and prevalence rates of circadian rhythm sleep disorders are not known, but 25% of all chronic sleep disorders are the result of a mismatch between the body's internal clock and the

Classification	General criteria or features	Prevalence
	Common symptoms for these types of disorders include Difficulty initiating and/or maintaining sleep, nonrestorative sleep, daytime sleepiness, poor concentration, impaired performance, including a decrease in cognitive skills, poor psychomotor coordination, headaches and gastrointestinal distress.	external 24-hour schedule. – **Medindia (2009)** • More than 35 million Americans suffer from circadian rhythm disorders. – **Medindia (2009)**
Parasomnias	These types of disorders are undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousals from sleep. Parasomnias encompass abnormal sleep-related movements, behaviors, emotions, perceptions, dreaming, and autonomic nervous system functioning. Parasomnias are clinical disorders because of the resulting untoward psychosocial effects. Parasomnias can affect the patient, the bed partner, or both. Common symptoms include snorting, headaches, loss of muscle control (cataplexy), poor concentration and focus, difficulty with memory, impaired motor coordination, irritability and impaired social interaction.	• **Nightmare disorder:** Unknown prevalence, although up to 50% of adults report occasional nightmares. – **Sharma (2007);** Affects about 2-8% of people. About 50-85% of adults report having at least an occasional nightmare. – **AASM (2008b)** • **Sleep Terror:** Information is limited at best. The DSM-IV estimates the prevalence rate in adults to be less than 1%. – **Sharma (2007);** About 2% of adults have sleep terrors. – **AASM (2008b)** • **Sleepwalking:** Episodes of the disorder have been documented in as many as 7% of clinical samples of adults. – **Sharma (2007)** • **Confused arousals**: occur in about 4% of adults. – **AASM (2008b)** • **REM sleep behavior disorder:** Prevalence not known. – **Sharma (2007);** Less than 1% of the population. – **AASM (2008b)**
Sleep Related Movement Disorders	These disorders are conditions that are primarily characterized by relatively simple, usually stereotyped, movements that disturb sleep. Rest Leg Syndrome, although not involving stereotyped movements per se, is classified here mainly because of its close association with Periodic Limb Movement Disorder. Prerequisites for a diagnosis are: • Nocturnal sleep disturbance • Daytime sleepiness or fatigue	• **Restless Leg Syndrome:** As high as 10% in general population and increases with age. – **Sharma (2007)** • **Periodic Limb Movement Disorder:** 5% of population aged 30 to 50 years, compared to 30% of population older than 50 years and 40% of population over 65. – **Sharma (2007)**

Source: AASM (2005)

Hypersomnias of Central Origin Not Due to a Circadian Rhythm Sleep Disorder, Sleep Related Breathing Disorder, or Other Cause of Disturbed Nocturnal Sleep

This subsection provides an overview of disorders in which the primary complaint is daytime sleepiness and in which the cause of the primary symptom is not disturbed nocturnal sleep or misaligned circadian rhythms. Estimated to afflict about 9 percent of the adult population (Hublin et al., 1996), daytime sleepiness is defined as the inability to stay awake and alert during the major waking episodes of the day, resulting in unintended lapses into drowsiness or sleep. The severity of daytime sleepiness can be quantified subjectively using severity scales such as the ESS and objectively using the MSLT and MWT. These measures are poorly correlated with each other and must be used with appropriate clinical judgment.

There are two main categories of hypersomnia:

- **Primary hypersomnia** does not have a known cause and is a chronic condition.
- **Secondary hypersomnia** may be traced to medical conditions (e.g., narcolepsy), physical injury and use of certain medications (e.g., tranquilizers).

Hypersomnia is considered to be a less common sleep disorder than insomnia and is most likely to first occur in people during adolescence and young adulthood.

Types

Narcolepsy With Cataplexy

Narcolepsy with cataplexy is a disabling sleep disorder affecting 0.02 percent of adults worldwide. It is characterized by severe, irresistible daytime sleepiness and sudden loss of muscle tone (cataplexy), and can be associated with sleep-onset or sleep-offset paralysis and hallucinations, frequent movement and awakening during sleep, and weight gain.

Narcolepsy Without Cataplexy

EDS is most typically associated with naps that are refreshing in nature while nocturnal sleep is normal or moderately disturbed without excessive amounts of sleep. Sleep paralysis, hypnagogic hallucinations or automatic behavior may be present.

Narcolepsy Due to Medical Condition

The direct cause of this disorder is a coexisting medical or neurological disorder. It must be documented clinically or polysomnographically. Daytime sleepiness is associated, and some have sleep paralysis, hypnagogic hallucinations or automatic behavior.

Recurrent Hypersomnia

A rare condition, the best-characterized recurrent hypersomnia is Kleine-Levin syndrome. These patients have recurrent episodes of hypersomnia often associated with other symptoms that typically occur wks or months apart. Episodes usually last a few days to several wks and appear once to 10 times a year. Episodes are often preceded by fatigue or a headache lasting a few hours. Patients may sleep as long as 16 to 18 hours a day.

Idiopathic Hypersomnia With Long Sleep Time

This is a disorder of severe sleepiness. It causes a person to have disabling daytime sleepiness, and it occurs despite an increased nightly sleep time of more than 10 hours. People with this disorder may sleep 12 to 14 hours every night with few interruptions. Even after sleeping this long time at night, it is very hard for them to wake up. Once awake, they may appear to be partially asleep, confused or drunk. This is called sleep drunkenness. Confusion and sleep drunkenness are common after morning awakening and also after naps.

Idiopathic Hypersomnia Without Long Sleep Time

This disorder is similar to Idiopathic Hypersomnia With Long Sleep Time but night sleep is either normal duration or slightly prolonged but less than 10 hours.

Behaviorally Induced Insufficient Sleep Syndrome

This disorder occurs when a person regularly fails to get enough sleep at night. The result is sleep deprivation. It keeps a person from feeling alert and well rested during the day. Considered a voluntary, but unintentional disorder, a person is normally unaware that he or she needs more sleep. An exam also shows that the person is able to sleep well when given the chance. It also detects no medical reason for the person to be sleepy. A mental exam also reveals nothing abnormal.

Hypersomnia Due to Medical Condition

This condition occurs when a person is sleepy due to a medical illness or a problem involving the nerves or brain. The person is tired no matter how much sleep he or she gets. If the medical problem or the nerve disorder goes away, then so does the sleepiness. There are many different medical problems that can cause sleepiness. These are just a few examples: Parkinson Disease, head trauma, brain tumors, brain infections, and kidney failure. Many of these problems can occur at any age and in either gender. This means that virtually anyone can get this disorder.

Hypersomnia Due to Drug or Substance (Abuse and for Alcohol Use)

This condition causes a person to feel an excessive level of sleepiness. It results from the abuse of alcohol, street drugs, or even properly prescribed drugs from a doctor. People with this problem usually abuse sleeping pills, or sedatives, and also alcohol.

Hypersomnia Due to Drug or Substance (Medications)

Daytime sleepiness may result from medications, such as antiepileptic medications and opioid analgesics.

Hypersomnia Not Due to Substance or Known Physiological Condition

This disorder is characterized by excessive nocturnal sleep, daytime sleepiness, or excessive napping, which is generally found not restorative. Patients are typically focused on their hypersomnia, and psychiatric symptoms typically become apparent only after prolonged interviews or psychometric testing. This disorder accounts for 5 percent to 7 percent of hypersomnia cases and appears more common in women 20 to 50 years old.

Risk Groups

- Likely to first occur in people during adolescence and young adulthood
- Hereditary link
- Medical problems: head injuries, tumors or damage to the central nervous system depression, bipolar disorder, epilepsy, heart problems, hypercalcemia, hyperthyroidism, liver problems, lung problems, multiple sclerosis, obesity and brain infections (e.g., meningitis, encephalitis).
- Autonomic nervous system dysfunction: The autonomic nervous system regulates physiologic processes in the body that are not under a person's control, such as blood pressure. When this system is impaired, it can lead to hypersomnia.
- Chronic fatigue syndrome: This is condition in which a patient experiences prolonged tiredness that is not relieved by rest. Hypersomnia often is associated with this condition.
- Drug or alcohol abuse: Use of various illegal and legal drugs and medications can cause hypersomnia. For example, patients who abuse sleep-aid drugs may experience chronic drowsiness.

Effects

- EDS
- Dreaming while awake
- Sleep paralysis
- Prolonged night-time sleep
- Hallucinations
- Intermittent manifestations of REM sleep during wakefulness
- Cataplexy
- Anxiety
- Decreased appetite
- Impaired memory
- Increased daytime hyperactivity in children
- Irritability and restlessness
- Slowed speech and thinking

Treatments

Treatment of narcolepsy is primarily directed at reducing EDS. Regular nocturnal sleep times with adequate time in bed is emphasized. In addition, scheduled daytime naps have been shown to improve the symptoms of severe daytime sleepiness. To enhance alertness further, pharmacologic therapy with stimulants is offered in a stepwise fashion.

- Therapy with modafinil is usually started first because of reasonable efficacy, a favorable side effect profile, and a lack of the peak and trough effects of shorter duration agents. Approved in 1998, this wake-promoting agent works via an unknown mechanism and appears to have minimal potential for addiction. Headache is the most common adverse reaction, but, unlike amphetamines, modafinil does not produce sympathomimetic effects.

- Conventional stimulants that increase synaptic amine availability, including methylphenidate, dextroamphetamine, and methamphetamine, are introduced if sleepiness persists with modafinil. Side effects such as palpitations and anxiety are not uncommon, and must be weighed against the benefits of increased alertness. High-dose stimulants carry a risk of side effects, such as weight loss and psychiatric disturbances.
- Cataplexy has traditionally been controlled with tricyclic antidepressants, and more recently with selective serotonin reuptake inhibitors and venlafaxine. The approval in 2002 of sodium oxybate for the treatment of cataplexy adds another treatment option. The drug binds γ-hydroxybutyrate, and, to a lesser extent, γ-amino butyric acid-B receptors in the brain. It is taken at bedtime and again 2.5 to four hours later. Sodium oxybate may improve nocturnal sleep continuity and increase slow-wave sleep. Patients with narcolepsy report improved daytime alertness when receiving therapy with the drug, and sodium oxybate received additional U.S. Food and Drug Administration approval in late 2005 for the treatment of EDS in narcolepsy patients. Its potential for abuse was demonstrated in the street drug γ-hydroxybutyrate, and sodium oxybate is available only through a single central pharmacy. Side effects include dizziness, vomiting, sleep walking, and enuresis. It can also produce respiratory depression and should not be used with other sedatives.
- Attempts at immunomodulation in a limited number of narcoleptic patients have been reported. One pediatric case report utilizing prednisone demonstrated no benefit, and a woman receiving plasma exchange had short-lived relief of cataplexy. The response of five patients undergoing treatment with IV Ig was varied; three had marked improvement in cataplexy, but objective improvement in the results of testing of the maintenance of wakefulness was seen in only one patient.

Table A- 2: Diagnostic Criteria and Symptoms of Other Hypersomnia of Central Origin Disorders

Disorder/ICD-9 Code	Diagnostic Criteria	Symptoms or features	Alternate Names
Narcolepsy With Cataplexy 347.01	• The patient has a complaint of EDS occurring almost daily for at least three months. • A definite history of cataplexy, defined as sudden and transient episodes of loss of muscle tone triggered by emotions, is present. • The diagnosis of narcolepsy with cataplexy should, whenever possible, be confirmed by nocturnal polysomnography followed by an MSLT; the mean sleep latency on MSLT is less than or equal to 8 minutes and 2 or more SOREMPs are observed following sufficient nocturnal sleep (min. 6 hours) during the night prior to the test. Alternatively, hypocretin-1 levels in the CSF are less than normal or equal to 110 pg/mL or one-third of mean normal control values. • The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.	• Sleep paralysis • Hypnagogic hallucinations • Nocturnal sleep disruption • Memory lapse • Ptosis • Blurred vision • Diplopia • Increased BMI • RBD	Gelineau Syndrome
Narcolepsy Without Cataplexy 347.00	• The patient has a complaint of EDS occurring almost daily for at least three months. • Typical cataplexy is not present, although doubtful or atypical cataplexy-like episodes may be reported. • The diagnosis of narcolepsy without cataplexy must be confirmed by nocturnal polysomnography followed an MSLT; the mean sleep latency on MSLT is less than or equal to 8 minutes, and 2 or more SOREMPs are observed following sufficient nocturnal sleep (min. 6 hours) during the night prior to the test. • The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.	• Memory lapse • Ptosis • Blurred vision • Diplopia • Nightmares • RBD • Frequent nocturnal sleep disruption • Cataplexy-like episodes	NA
Narcolepsy Due to Medical Condition (Without Cataplexy 347.10) (**With Cataplexy** 347.11)	• The patient has a complaint of EDS occurring almost daily for at least three months. • One or more of the following must be observed: ○ Definite history of cataplexy; ○ If Cataplexy is not present or is very atypical, polysomnographic monitoring performed over the patient's habitual sleep period followed by an MSLT must demonstrate a mean sleep latency on the MSLT of less than 8 minutes with 2 or more SOREMPs, despite sufficient nocturnal sleep prior to the test (minimum 6 hours). ○ Hypocretin-1 levels in the CSF are less than 110 pg/mL (or 30 percent of normal control values), provided the patient is not comatose. • A magnificent underlying medical or neurological disorder accounts for the daytime sleepiness. • The hypersomnia is not better explained by another sleep disorder, mental	• Daytime sleepiness • Sleep paralysis • Hypnagogic hallucinations • Insomnia	Secondary narcolepsy, symptomatic narcolepsy

Disorder/ICD-9 Code	Diagnostic Criteria	Symptoms or features	Alternate Names
	disorder, medication use, or substance use disorder.		
Narcolepsy, Unspecified 347.00	This diagnosis is used on a temporary basis when the patient meets clinical and MSLT criteria for narcolepsy, but further evaluation is required to determine the specific diagnostic for narcolepsy.	NA	NA
Recurrent Hypersomnia (Including Kleine-Levin Syndrome and Menstrual-Related Hypersomnia) 327.13	• The patient experiences recurrent episodes of excessive sleepiness of two days to four wks duration. • Episodes recur at least once a year. • The patient has normal alertness, cognitive functioning and behavior between attacks. • The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.	• Fatigue • Headache • Body weight gain of a few kilograms • Cognitive abnormalities such as feelings of unreality, confusion, and hallucination • Binge eating • Hypersexuality • Irritability • Aggressiveness	Periodic hypersomnia
Idiopathic Hypersomnia With Long Sleep Time 327.11	• EDS occurring almost daily for at least three months. • The patient has prolonged nocturnal sleep time (more than 10 hours) documented by interview, actigraphy or sleep logs. Waking up in the morning or at the end of naps is almost always laborious. • Nocturnal polysomnography has excluded other causes of daytime sleepiness. • The polysomnogram demonstrates a short sleep latency and a major sleep period that is prolonged to more than 10 hours in duration. • If an MSLT is performed following overnight polysomnography, a mean sleep latency of less than 8 minutes is found, and fewer than 2 SOREMPs are recorded. Mean sleep latency in idiopathic hypersomnia with long sleep time has been shown to be 6.2 $\pm$ 3.0 minutes. • The sleep disorder is not better explained by another sleep disorder, medical or neurological disorder, or mental disorder. ***Note:*** *Of particular importance, head trauma should not be considered to be the cause of the sleepiness.*	• Constant and severe sleepiness with prolonged but unrefreshing naps of up to three or four hours. • Post-awakening confusion and difficulty waking up • Nocturnal sleep of 10 or more hours	NA
Idiopathic Hypersomnia Without Long Sleep Time 327.12	• EDS occurring almost daily for at least three months. • Patient has normal nocturnal sleep • Nocturnal polysomnography has excluded other causes of daytime	• Severe daytime sleepiness • Normal nocturnal sleeping	NA

Disorder/ICD-9 Code	Diagnostic Criteria	Symptoms or features	Alternate Names
	sleepiness. • Polysomnography demonstrates a major sleep period that is normal in duration (greater than 6 hours and less than 10). • An MSLT following overnight polysomnography demonstrates a mean sleep latency of less than 8 minutes and fewer than 2 SOREMPs. • Insomnia clearly associated with the medical or physiologic condition. • The sleep disorder is not better explained by another sleep disorder, mental disorder, medication use or substance abuse disorder. Mean sleep latency in idiopathic hypersomnia with long sleep time has been shown to be 6.2 ± 3.0 minutes. • The sleep disorder is not better explained by another sleep disorder, medical or neurological disorder, or mental disorder.		
Behaviorally Induced Insufficient Sleep Syndrome 307.44	• Excessive sleepiness for at least three months. • Habitual sleep episode usually shorter than expected from age-adjusted normative data. • When habitual sleep schedule is not maintained (weekends or vacation time), individual sleeps considerably longer than usual. • When polysomnography performed, sleep latency is less than 10 minutes and sleep efficiency greater than 90 percent. During an MSLT, a short mean sleep latency of less than 8 minutes may be observed. • The sleep disorder is not better explained by another sleep disorder, medical or neurological disorder, or mental disorder.	• Irritability • Concentration and attention deficits • Reduced vigilance • Distractibility • Reduced motivation • Anergia • Dysphoria • Fatigue • Restlessness • Incoordination • Malaise • Sleep paralysis • Hypnagogic hallucinations	NA
Hypersomnia Due to Medical Condition 327.14	• Excessive sleepiness for at least three months. • A significant underlying medical or neurological disorder accounts for the daytime sleepiness. • If an MSLT is performed, the mean sleep latency is less than 8 minutes with no more than 1 SOREMP following polysomnographic monitoring performed over the patient's habitual sleep period, with a minimum total sleep time of 6 hours. • The sleep disorder is not better explained by another sleep disorder, mental disorder, medication use, or substance abuse disorder.	• Daytime sleepiness varies in severity and may resemble narcolepsy • Sleep paralysis • Hypnagogic hallucinations • Automatic behavior • Long sleep episode and unrefreshing sleep	NA
Hypersomnia Due to Drug or Substance (**Abuse** 292.85) (**For Alcohol use** 291.82)	• Excessive sleep • Complaint is believed to be secondary to current use, recent discontinuation, or prior prolonged use of drugs. • The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, or medication use.	• Excessive nocturnal sleep • Daytime sleepiness • Excessive daytime naps	NA
Hypersomnia Due to Drug or	• Excessive sleep	• Excessive nocturnal sleep • Daytime sleepiness	NA

Disorder/ICD-9 Code	Diagnostic Criteria	Symptoms or features	Alternate Names
Substance (Medications) 292.85	• Complaint is associated with current use, recent discontinuation, or prior prolonged use of a prescribed medicine. • The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, or medication use.	• Excessive daytime naps	
Physiological Condition (Nonorganic Hypersomnia, NOS) 327.15	• Excessive sleep, day or night • Complaint is associated with a psychiatric diagnosis. • Polysomnographic monitoring demonstrates both of the following: ○ Reduced sleep efficiency and increased frequency and duration of awakenings ○ Variable, often normal, mean sleep latencies on the MSLT • The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, or medication use.	• Excessive nocturnal sleep • Daytime sleepiness • Excessive daytime naps • Causative psychiatric conditions: mood disorders, conversion or undifferentiated somatoform disorder • Poor work attendance • Lack of interest and social withdrawal • Decreased energy level	Hypersomnia associated with mental disorders, psychiatric hypersomnia, secondary hypersomnia (psychiatric), sleep hypochondriasis, pseudohypersomnia or pseudonarcolepsy
Physiological (Organic) Hypersomnia, Unspecified (Organic Hypersomnia, NOS) 327.10	Disorders that satisfy clinical criteria (a complaint of excessive sleepiness occurring almost daily for at least three months) and MSLT criteria (mean sleep latency less than 8 minutes with fewer than 2 SOREMPs) for hypersomnolence and are believed to be due to a physiological condition, but do not meet criteria for other hypersomnolence conditions, are classified here.	NA	NA

Source: AASM (2005)

Appendix B: Medical-related State Regulations and Guidelines

Table B- 1. Medical-related State Regulations and Guidelines for Sleep, Sleep Disorder, and/or Fatigue

State	Commercial		Private	
	Specific criteria? 1= yes; 2= no; 3=not stated; 4=default to federal regulations			
	Details			Details
Alabama	2	You should consult your physician or a local sleep disorder center if you suffer from frequent daytime sleepiness, have difficulty sleeping at night, take frequent naps, fall asleep at strange times, snore loudly, gasp and choke in your sleep, and/or wake up feeling as though you have not had enough sleep.	2	
Alaska	2	You should consult your physician or a local sleep disorder center if you suffer from frequent daytime sleepiness, have difficulty sleeping at night, take frequent naps, fall asleep at strange times, snore loudly, gasp and choke in your sleep, and/or wake up feeling as though you have not had enough sleep.	2	You must control yourself before you can control a vehicle. Driving with insufficient sleep, anger, or distractions are examples of factors that will impair your ability to safely control a vehicle.
Arizona	2	You should consult your physician or a local sleep disorder center if you suffer from frequent daytime sleepiness, have difficulty sleeping at night, take frequent naps, fall asleep at strange times, snore loudly, gasp and choke in your sleep, and/or wake up feeling as though you have not had enough sleep.	2	Driver's manual states people with sleep disorders are among five identified groups more likely to have collisions caused by sleepiness and advises getting rest, changing drivers, not driving late at night, taking rest stops, etc.
Arkansas	2	**Fatigue and Lack of Alertness.** Fatigue (being tired) and lack of alertness are bigger problems at night. The body's need for sleep is beyond a person's control. Most people are less alert at night, especially after midnight. This is particularly true if you have been driving for a long time. Drivers may not see hazards as soon or react as quickly, so the chance of a crash is greater. If you are sleepy, the only safe cure is to get off the road and get some sleep. If you don't, you risk your life and the lives of others.	2	**Fatigue** When you are tired, you cannot drive as safely as when you are rested and you do not see as well nor are you as alert as when you are rested. It takes you more time to make decisions and you do not always make good decisions. You can be more irritable and can get upset more easily. Lastly, when you are tired, you could fall asleep behind the wheel and crash. There are things you can do to keep from getting tired on a long trip. • Try to get a good night's sleep before you leave. • Do not leave on a trip if you are tired. Plan your trips so you can leave when you are rested. • Do not take any medicine that might make you drowsy. • Eat light meals prior to departure. Large, full meals tend to cause drowsiness. • Take breaks. Stop, regularly, or when needed. To walk around, get fresh air, and refresh yourself with some coffee, soda, or juice. The few minutes spent on a rest break can save your life. Plan for plenty of time to complete your trip safely. • Avoid long trips during hours your body is accustomed to resting. • Never drive if you are sleepy. It is better to stop and sleep for a few hours

State	Commercial		Private	
Specific criteria? 1= yes; 2= no; 3=not stated; 4=default to federal regulations				
				than take a chance you can stay awake.
California	2	CDL applicants must have medical certificate in accordance with 49 CFR 391.41	2	If you are tired all the time and fall asleep often during the day, ask your physician to check for a sleep disorder.
Colorado	2	If you are sleepy, the only safe cure is to get off the road and get some sleep. If you do not, you risk your life and the lives of others. Each applicant shall meet the medical and physical qualifications under FMCSR Part 391.41 and have this examination verified on a DOT medical examination form. Unless the following exceptions apply, each driver shall carry this medical examination form or the medical examiner's certificate on his/her person when operating a CMV.	2	No mention found.
Connecticut	2	Sleep disorders, pauses in breathing while asleep, daytime sleepiness, loud snoring. FOR ANY "YES" ANSWER, INDICATE ONSET DATE, DIAGNOSIS, TREATING PHYSICIAN'S NAME AND ADDRESS, AND ANY CURRENT LIMITATION. LIST ALL MEDICATIONS (Including over-the-counter medications) used regularly or recently.—from CT DMV examination to determine physical condition of driver—R-323 Rev. 3-2004.	2	**Fatigue** You cannot drive as safely when you are tired as when you are rested. You do not see as well, nor are you as alert. It takes you more time to make decisions, and you may not always make good decisions. You can be more irritable and can get upset more easily. When you are tired, you could fall asleep behind the wheel and crash, injuring or killing yourself or others. There are things you can do to help from getting tired on a long trip: • Try to get a normal night's sleep before you leave. • Do not leave on a trip if you are already tired. Plan your trips so you can leave when you are rested. • Do not take any medicine that can make you drowsy. • Eat lightly. Do not eat a large meal before you leave. Some people get sleepy after they eat a big meal. • Take breaks. Stop every hour or so when you need to. Walk around, get some fresh air, and have some coffee, soda, or juice. The few minutes spent on a rest break can save your life. Plan for plenty of time to complete your trip safely. • Try not to drive late at night when you are normally asleep. Your body thinks it is time to go to sleep and will try to do so.
Delaware	2	No mention of sleep disorders, just advice to get enough sleep, to pull over and nap if sleepy while driving, and to avoid taking drugs that make a person sleepy.	2	Driver's manual provides tips on driving rested, taking breaks if tired, but makes no mention of sleep disorders.
District of Columbia	4	Requires valid and stamped U.S. Department of Transportation Medical Examination Report/Medical Card and Medical Examiner's Certificate.	2	No mention of sleep disorders in new or renewal license information.
Florida	4	Must be in compliance with the vision and physical requirements as stated in Part 391 of the Federal Motor Carrier Safety Regulations Handbook	3	Physical and Mental Requirements You must list any physical or mental problems on your license application that might affect your driving. Many of the physical problems can be handled by

State	Commercial		Private	
	Specific criteria? 1= yes; 2= no; 3=not stated; 4=default to federal regulations			
				placing restrictions on your license. If you have epilepsy, fainting spells, dizziness, blackouts or any other medical condition that could impair your driving, you may be asked to have your doctor complete a medical report form. These forms may be requested through your local driver licenses office and are mailed directly to you. The report must be completed by your doctor and submitted to the Department before a license is issued. If you are diabetic and use insulin, you may request that "Insulin Dependent" is indicated on your license.
Georgia	4	Requires U.S. DOT Medical Examiner's Certificate	2	Applicants must have physicians fill out a medical report form, but no questions pertain to sleep disorders.
Hawaii	4	Requires U.S. DOT Medical Examiner's Certificate	2	No mention of sleep or sleep disorders found.
Idaho	4	No mention of sleep or sleep disorders found. Requires U.S. DOT Medical Examiner's Certificate	2	No mention of sleep disorders, but caution to pull over and nap if drowsy while driving.
Illinois	4	Requires U.S. DOT Medical Examiner's Certificate	2	By law, you are required to file a Medical Report Form, completed by your physician, if: you have any medical or mental condition which could result in a loss of consciousness or any loss of ability to safely drive a vehicle.
Indiana	4		3	The applicant must submit an original medical examination form 3337. The form must be completed…by a licensed physician indicating that the applicant does not suffer any mental or physical impairments that would adversely affect the applicant's ability to operate a public passenger vehicle.
Iowa	4		2	No mention of sleep or sleep disorders found
Kansas	4		2	No mention of sleep or sleep disorders found
Kentucky	3	No mention of sleep disorders found.	2	No mention of sleep or sleep disorders found
Louisiana				
Maine	4	Requires drivers to certify they meet the federal medical standards.	3	No mention of sleep disorders among those medical conditions requiring a functional ability driving evaluation form.
Maryland	4	Requires DOT physical card.	3	No mention of sleep disorders
Massachusetts	3	No mention of sleep disorders.	3	No mention of sleep disorders.
Michigan	4	Unless exempt, you need to comply with federal or state medical/physical requirements before receiving a CDL. When applying for your CDL, you will sign a statement that says all necessary medical/physical requirements have been met. Before taking any CDL skills tests, you must provide a valid medical	3	No mention of sleep disorders, but driver's manual states that certain medical conditions (unspecified) could result in a restricted license.

State	Commercial		Private	
	Specific criteria? 1= yes; 2= no; 3=not stated; 4=default to federal regulations			
		examiner's card or medical waiver card to your examiner which allows you to operate your commercial motor vehicle.		
Minnesota	4	Requires DOT medical card.	3	No mention of sleep disorders.
Mississippi	3		3	
Missouri	4	Must be medically qualified and certified per FMCSA standards.	2	Medical Referral There are two reasons you may need a physician's statement when you renew or apply for a license: • You have had epileptic seizures, convulsions, or blackouts within the six months prior to your application for a license. • A driver examiner, license clerk, family member, law enforcement officer, or physician believes you may have some other medical condition that would make you an unsafe driver. This person must complete the Driver Condition Report (Form 4319) and submit it to the Department of Revenue.
Montana	4	Must submit DOT card	2	No mention found of sleep disorders
Nebraska	4	Individuals applying for a Nebraska School Bus Permit are required to present a Department of Transportation Medical Examination Report. Forms are available by clicking on “Forms and Pubs” at the following website: www.fmcsa.dot.gov/.	3	
Nevada	4	You have to be physically examined by a U.S. licensed physician every two years. The doctor will give you a medical report and will fill out and sign a medical certificate for you to carry with your CDL. The medical certificate must be presented when applying for your commercial driver license. You can be cited by law enforcement if you drive commercially with an out-dated medical certificate, or if you do not have a current one with you. To ensure accurate records, your medical certificate must be filed with the Nevada Department of Motor Vehicles every two years or less if required by your physician.	2	No mention of any medical requirements, but possibility of a medically restricted license.
New Hampshire	4	Must comply with FMCSR Part 391 or apply for an intrastate waiver. Those driving intrastate only must also comply with FMCSA Part 391 or apply for a state waiver.	3	Vision only medical requirement mentioned
New Jersey	3		2	Applicants are required to inform the examiner of any serious health problems. In certain cases, a medical review may be necessary. The examiner will discuss this with the applicant. Under federal law, commercial drivers must carry a medical examiner’s fitness statement and have it renewed every two years.
New Mexico	4	You must be physically capable of obtaining a valid medical examiner's card (before taking any CDL skills test).	3	In New Mexico drivers who have epilepsy, diabetes, adverse heart conditions and other medical problems are required to send the Motor Vehicle Division

State	Commercial		Private	
Specific criteria? 1= yes; 2= no; 3=not stated; 4=default to federal regulations				
				periodic medical statements signed by their physicians. Consult the Motor Vehicle Division for more information
New York	4	Drivers are required to hold a DOT medical card. CDL driver manual warns drivers who experience daytime sleepiness or other listed symptoms to seek help from a medical specialist for an undiagnosed sleep disorder.	1	New York state driver's license applicants must have a physician fill out a Physician's Statement for Medical Review Unit that includes a question on sleep disorders. If the physician answers yes, there are follow-up questions on date of diagnosis, whether the patient is being treated, type of treatment, date treatment began and whether patient is compliant. In addition, the driver's manual states: People With Undiagnosed Sleep Disorders — The presence of a sleep disorder also increases the risk of crashes. If you find you are regularly tired during the day or experience any of these symptoms on a regular basis, you may have a sleep disorder and should seek medical help.
North Carolina	4	Many commercial motor-vehicle drivers are required to have medical cards. Those who require medical cards are required to bring them at the time of both the original application and renewal. Commercial motor-vehicle driver operating out-of-state must hold a current NCDOT Medical Card certifying that he or she has passed a physical examination, as required by the ICC. You must have no physical or mental illness that interferes with your ability to control and operate a motor vehicle. You must have no established medical history or clinical diagnosis of epilepsy or any other condition which is likely to cause loss of consciousness or any loss of ability to control a motor vehicle. To operate a commercial motor vehicle, you must have no mental nervous, organic, or functional diseases or psychiatric disorder likely to interfere with your ability to drive a motor vehicle safely.	2	Driver's manual states people with sleep disorders are at increased risk of crash.
North Dakota	4	No mention of sleep disorders.	3	No mention of sleep disorders in driver's manual.
Ohio	4	No mention of sleep disorders.	3	No mention of sleep disorders in driver's manual.
Oklahoma	3	No mention of sleep disorders.	3	No mention of sleep disorders in driver's manual.
Oregon	4	To qualify for a commercial driver license (CDL) you must pass a Department of Transportation (DOT) medical examination performed in accordance with CFR 49 §391.41 and CFR 49 §391.43.	3	No mention of sleep disorders in driver's manual, but a caution to pull over if drowsy while driving.
Pennsylvania	4		3	PennDOT has a Medical Advisory Board that is responsible for the formulation of physical and mental criteria, including vision standards, for the licensing of drivers. The Board consists of a neurologist, a cardiologist, an internist, a general practitioner, an ophthalmologist, a psychiatrist, an orthopedic surgeon, an optometrist, and members from PennDOT, Department of Justice, Department of Health and the Pennsylvania State Police. The formulation of

State	Commercial		Private	
	Specific criteria? 1= yes; 2= no; 3=not stated; 4=default to federal regulations			
				these regulations is open for public review and comment through the Commonwealth's Regulatory Review process. Pennsylvania law Inattentiveness to the task of driving because of, for example, preoccupation, hallucination or delusion. (ii) Contemplation of suicide, as may be present in acute or chronic depression or in other disorders. (iii) Excessive aggressiveness or disregard for the safety of self or others or both, presenting a clear and present danger, regardless of cause. (6) Periodic episodes of loss of attention or awareness which are of unknown etiology or not otherwise categorized, unless the person has been free from episode for the year immediately preceding, as reported by a licensed physician. (7) Use of any drug or substance, including alcohol, known to impair skill or functions, regardless whether the drug or substance is medically prescribed. (8) Other conditions which, in the opinion of a provider, is likely to impair the ability to control and safely operate a motor vehicle. (c) Driving examination. A person who has any of the conditions enumerated in subsection (b)(1), (2), (3) or (8) may be required to undergo a driving examination to determine driving competency, if the Department has reason to believe that the person's ability to safely operate a motor vehicle is impaired.
Rhode Island	2	You should consult your physician or a local sleep disorder center if you suffer from frequent daytime sleepiness, have difficulty sleeping at night, take frequent naps, fall asleep at strange times, snore loudly, gasp and choke in your sleep, and/or wake up feeling as though you have not had enough sleep	3	
South Carolina	3	Unable to access CDL manual and no search function on DMV data base.	3	Unable to access driver's manual, but general description gives no medical requirements, and no search function on DMV site.
South Dakota	3	Although the manual offers the possibility of a medically restricted license, no medical conditions or medical standards are listed.	3	Although the manual offers the possibility of a medically restricted license, no medical conditions or medical standards are listed.
Tennessee	4	You must have a current, valid medical card	3	No mention of sleep disorders or any other medical disqualifiers..
Texas	3		3	Applicants must provide answers to medical status and history questions listed on application form. Persons with certain medical limitations may have their cases reviewed by the Texas Medical Advisory Board for Driver Licensing before the license may be issued,
Utah	3	Cautions against drowsy driving, avoiding medications, and emphasizes the importance of recognizing the signals of sleepiness. Advises drivers consult a physical or local or a local sleep disorder center if you suffer from frequent	1	Utah has guidelines and standards for health care professionals in assessing license applicants' functional abilities in driving. Category K covers alertness or sleep disorders. All applicants for licenses will complete a health questionnaire

State	Commercial		Private	
	Specific criteria? 1= yes; 2= no; 3=not stated; 4=default to federal regulations			
		daytime sleepiness, have difficulty sleeping at night, take frequent naps, fall asleep at strange times, snore loudly, gasp and choke in your sleep, and/or wake up feeling as though you have not had enough sleep.		to show their functional ability to drive. If there is a significant health problem, they will take their medical form to a health care professional, who will profile the category for the condition indicated or change it to be consistent with the true medical situation. The health care professional will be expected to discuss the applicant's health as it relates to driving and to make special recommendations in unusual circumstances. Based on a completed Functional Ability Evaluation form, the Driver License Division may issue a license with or without limitations.
Vermont	3	Cautions against drowsy driving, avoiding medications, and emphasizes the importance of recognizing the signals of sleepiness. Advises drivers consult a physical or local or a local sleep disorder center if you suffer from frequent daytime sleepiness, have difficulty sleeping at night, take frequent naps, fall asleep at strange times, snore loudly, gasp and choke in your sleep, and/or wake up feeling as though you have not had enough sleep.	2	No mention of sleep disorders.
Virginia	4	Default to federal regulations	2	No mention of sleep disorders.
Washington	1	Medical examination form for commercial driver fitness asks if applicant has sleep disorders, pauses in breathing during sleep, loud snoring, or daytime sleepiness. A yes answer requires a date of onset, physician's name and address, and any current limitation.	1	Will ask driver's license applicants if they have a mental or physical condition or are taking any medications that might impair their ability to drive. If the answer is yes, the department may require examination by a medical specialist.
West Virginia	4	Federal Motor Carrier Rules requires that drivers subject to those rules meet specific physical qualification standards and carry evidence of such qualification in the form of a medical certificate.	1	You should consult your local physician or a sleep disorder center if you suffer from frequent daytime sleepiness, have difficulty sleeping at night, take frequent naps, fall asleep at strange times, snore loudly, choke or gasp in your sleep, and/or wake up feeling as if you have not had enough sleep.
Wisconsin	1	For school bus or passenger endorsement, applicants with a diagnosis of sleep apnea must present a physician's statement indicating treatment has been successful and the condition will not impair ability to safely operate a commercial vehicle.	2	No mention of sleep disorders, just a warning against driving while fatigued.
Wyoming	1	You should consult your local physician or a sleep disorder center if you suffer from frequent daytime sleepiness, have difficulty sleeping at night, take frequent naps, fall asleep at strange times, snore loudly, choke or gasp in your sleep, and/or wake up feeling as if you have not had enough sleep.	2	No mention of sleep disorders.

Web Resources for State Data

Alabama

DMV website *www.dps.state.al.us/*

http://www.dps.state.al.us/DriverLicense/manuals/cdlmanual.pdf

http://www.dps.state.al.us/DriverLicense/manuals/DriverManual.pdf

Alaska

DMV website: http://www.state.ak.us/

http://google.state.ak.us/search?q=cache:YMPrS6qsdkYJ:www.state.ak.us/local/akpages/ADMIN/dmv/cdlmanual/manual.pdf+sleep+disorder&access=p&output=xml_no_dtd&site=DMV&ie=UTF-8&client=DMV&proxystylesheet=StateWide&oe=UTF-8

http://www.state.ak.us/local/akpages/ADMIN/dmv/dlmanual/dlman.pdf

Arizona

DMV website: http://www.dot.state.az.us

www.azdot.gov/mvd/documents/CustomerServiceGuide_99-0117.pdf

http://mvd.azdot.gov/mvd/formsandpub/viewPDF.asp?lngProductKey=567&lngFormInfoKey=567

Arkansas

DMV website: http://www.arkansas.gov/

http://www.asp.state.ar.us/divisions/hp/pdf/cdl_manual_2003.pdf

http://www.asp.state.ar.us/divisions/hp/pdf/dl_study_guide_0704_rev.pdf

California

DMV website: http://www.dmv.ca.gov/

http://www.dmv.ca.gov/forms/dl/dl51.pdf

http://www.dmv.ca.gov/pubs/hdbk/hlth_safety.htm

Colorado

DMV website:http://www.colorado.gov/revenue

http://www.colorado.gov/cs/Satellite?blobcol=urldata&blobheader=application%2Fpdf&blobheadername1=Content-Disposition&blobheadername2=MDT-Type&blobheadervalue1=inline%3B+filename%3D714%2F305%2F2005_CDLFinal_Manual122105+margaret%2C0.pdf&blobheadervalue2=abinary%3B+charset%3DUTF-8&blobkey=id&blobtable=MungoBlobs&blobwhere=1191399221447&ssbinary=true

http://www.sos.state.co.us/CCR/Rule.do?deptID=19&deptName=200%20Department%20of%20Revenue&agencyID=76&agencyName=204%20Division%20of%20Motor%20Vehicles&ccrDocID=1957&ccrDocName=1%20CCR%20204-12%20RULES%20AND%20REGULATIONS%20FOR%20COMMERCIAL%20DRIVER'S%20LICENSE%20(CDL)&subDocID=40471&subDocName=D.%20%20APPLICANT%20LICENSING%20REQUIREMENTS%20[Eff.%2011/30/2008]&version=2

Connecticut

DMV website: http://www.ct.gov/

http://www.ct.gov/dmv/LIB/dmv/20/29/R-323.pdf

http://www.ct.gov/dmv/lib/dmv/20/29/ctdriver.pdf

Delaware

DMV website: http://www.dmv.de.gov/

http://www.dmv.de.gov/forms/driver_serv_forms/pdfs/dr_frm_cdlmanual_revised_050907.pdf

http://www.dmv.de.gov/forms/driver_serv_forms/pdfs/dr_frm_manual_08182006r.pdf

District of Columbia

DMV website: http://dmv.washingtondc.gov/

http://dmv.washingtondc.gov/serv/dlicense/commercial_howto.shtm
http://dmv.washingtondc.gov/serv/dlicense/DLrenewal.shtm

Florida

DMV website: http://www.hsmv.state.fl.us/
http://www.flhsmv.gov/handbooks/
http://www.lowestpricetrafficschool.com/handbooks/cdl/en/1/3

Georgia

DMV website: http://www.dds.ga.gov//
http://www.dds.ga.gov/docs/forms/DS-287.pdf
http://www.dds.ga.gov/FormsandManuals/index.aspx#Manuals

Hawaii

DMV website: http://www.state.hi.us/
http://www6.hawaii.gov/dot/highways/hwy-v/cdl_apply.pdf
http://www6.hawaii.gov/dot/highways/hwy-v/HIDrvMan.pdf

Idaho

DMV website: http://www.itd.idaho.gov/
http://itd.idaho.gov/dmv/MotorCarrierServices/mc_qual.htm
http://www.itd.idaho.gov/dmv/DriverServices/documents/cdl_manual.pdf
http://www.itd.idaho.gov/dmv/DriverServices/documents/driver_manual.pdf

Illinois

DMV website: http://www.sos.state.il.us/
http://www.sos.state.il.us/departments/drivers/drivers_license/medical_vision.html
http://www.itd.idaho.gov/dmv/DriverServices/documents/cdl_manual.pdf

Indiana

DMV website: http://www.in.gov/
http://www.in.gov/bmv/3250.htm
http://www.in.gov/bmv/files/Indiana_Driver_Manual_-_Chapter_One.pdf

Iowa

DMV website: http://www.iamvd.com/
http://www.iamvd.com/ods/dlmanual/section1.pdf

Kansas

DMV website: http://www.ksrevenue.org/
http://www.cdl-course.com/faq-ks.html

Kentucky

DMV website: http://transportation.ky.gov/
http://www.kentuckystatepolice.org/pdf/2006_ky_drivers_manual.pdf

Louisiana
DMV website: http://omv.dps.state.la.us/
Maine
DMV website: http://www.state.me.us/
http://www.maine.gov/search?q=CDL+medical&as_sitesearch=http%3A%2F%2Fwww.maine.gov%2Fsos%2Fbmv&site=test_collection&output=xml_no_dtd&client=test_collection&proxystylesheet=test_collection
http://www.maine.gov/sos/cec/rules/29/250/250c003.doc
Maryland
DMV website: http://www.mva.state.md.us/
http://www.mva.state.md.us/DriverServ/Apply/CDL/commercial.htm
http://www.mva.state.md.us/OnlineServices/Docs/default.htm
Massachusetts
DMV website: http://www.mass.gov/
http://www.mass.gov/rmv/medical/mabrochure.pdf

Michigan
DMV website: http://www.michigan.gov/
http://www.michigan.gov/sos/0,1607,7-127-1627_8666_9060-21614--,00.html
http://www.michigan.gov/documents/SOS_WEDMK_1_Michigan_Drivers_License_Information_158263_7.pdf
Minnesota
DMV website: http://www.dps.state.mn.us/
http://www.dps.state.mn.us/dvs/DLTraining/DLManual/PDF/08CDLManual.pdf
http://www.dps.state.mn.us/dvs/DriverLicense/DL%20Info/DL%20frame.htm
Mississippi
DMV website: http://www.dps.state.ms.us/
http://www.dps.state.ms.us/dps/dps.nsf/webFAQs/BD9DC256D817FB8A86256AF10057409D?OpenDocument
http://www.dps.state.ms.us/dps/dps.nsf/divpages/hp2ds-info-classR?OpenDocument
Missouri
DMV website: http://www.dor.mo.gov/mvdl/
http://dor.mo.gov/mvdl/drivers/forms/cdl.pdf
http://dor.mo.gov/mvdl/drivers/dlguide/chapter1.pdf
Montana
DMV website: http://www.doj.mt.gov/driving/driverlicensing.asp
http://mt.gov.cdc.nicusa.com/search?entqr=0&ud=1&sort=date%3AD%3AL%3Ad1&output=xml_no_dtd&oe=UTF-8&ie=UTF-8&client=Justice&proxystylesheet=Justice&site=Justice&q=CDL+medical
http://data.opi.mt.gov/bills/mca_toc/61_5_1.htm

Nebraska
DMV website: http://www.dmv.state.ne.us/
http://www.dmv.state.ne.us/examining/pdf/cdlmanual.pdf
http://www.dmv.state.ne.us/examining/pdf/engdrivermanual.pdf
Nevada
DMV website: http://www.dmvnv.com/
http://www.dmvnv.com//pdfforms/dlbookcomm.pdf
http://www.dmvnv.com/pdfforms/dlbook.pdf
New Hampshire
DMV website: http://nh.gov/
http://www.nh.gov/safety/divisions/dmv/documents/nhcdm.pdf
http://www.nh.gov/safety/divisions/dmv/driverlic/faq.html#A7
New Jersey
DMV website: http://www.state.nj.us/\
http://www.state.nj.us/mvc/pdf/Commercial/CDL_Manual_english.pdf
http://www.state.nj.us/mvc/manuals/chap_02_01.html
New Mexico
DMV website: http://www.state.nm.us/
http://www.cdl-course.com/faq-nm.html
New York
DMV website: http://www.nydmv.state.ny.us/
http://www.nysdmv.com/forms/mv80u1.pdf
http://www.nydmv.state.ny.us/license.htm#drivermed
http://www.nysdmv.com/broch/DM-04_07.pdf
North Carolina
DMV website: http://www.ncdot.org/
http://www.ncdot.gov/dmv/driver_services/commercialtrucking/requirements.html
http://www.ncdot.gov/dmv/driver_services/drivershandbook/download/NCDL_English.pdf
North Dakota
DMV website: http://www.state.nd.us/
http://www.dot.nd.gov/docs/class_c1.pdf
http://www.dot.nd.gov/docs/rulesroad.pdf
Ohio
DMV website: http://dmv.ohio.gov/
http://bmv.ohio.gov/driver_license/cdl.htm#Procedures
http://bmv.ohio.gov/driver_license/first_dl_exam.htm

Oklahoma
DMV website: http://www.dps.state.ok.us/
http://www.dps.state.ok.us/dls/pub/ODM.pdf
http://www.dps.state.ok.us/dls/pub/ODM.pdf
Oregon
DMV website: http://www.oregon.gov/ODOT/DMV
http://www.odot.state.or.us/forms/dmv/37.pdf
Pennsylvania
DMV website: http://www.dmv.state.pa.us/
http://www.dot3.state.pa.us/driverSafetyCenter/medicalCriteria.shtml
http://www.pacode.com/secure/data/067/chapter83/chap83toc.html
http://www.dot3.state.pa.us/pdotforms/dl_forms/dl-143cdi.pdf
Rhode Island
DMV website: http://www.dmv.state.ri.us/
http://www.dmv.state.ri.us/documents/manuals/CDL_Manual.pdf
http://www.dmv.state.ri.us/documents/manuals/Driver_Manual_FINAL.pdf
South Carolina
DMV website: http://www.scdmvonline.com/
http://www.scdmvonline.com/DLgeneral.aspx#GetDL
http://www.scdmvonline.com/forms/DriverManual/Eng_4_Trucks.pdf
South Dakota
DMV website: http://www.state.sd.us/drr2/motorvehicle/
http://www.state.sd.us/dps/dl/Online_Manuals/2005%20CDL%20MANUAL.pdf
http://www.state.sd.us/dps/dl/Online_Manuals/2005%20CDL%20MANUAL.pdf
Tennessee
DMV website: http://www.tennessee.gov/
http://tennessee.gov/safety/publications/CDLManual08.pdf
Texas
DMV website: http://www.txdps.state.tx.us
http://www.txdps.state.tx.us/ftp/forms/CDLhandbook.pdf
http://www.txdps.state.tx.us/administration/driver_licensing_control/faq/answers_dl_id.htm#q33
http://tennessee.gov/safety/dlhandbook/DL_HandbookWeb2007.pdf
Utah
DMV website: http://driverlicense.utah.gov/
http://publicsafety.utah.gov/dld/docs/2005%20CDL%20DRIVER%20MANUAL%20_Final_%20Revised%20Oct%202007.pdf
http://www.rules.utah.gov/publicat/bulletin/2009/20090101/32202.htm

http://publicsafety.utah.gov/dld/docs/functional_ability.pdf

Vermont

DMV website: http://www.aot.state.vt.us/

http://www.aot.state.vt.us/dmv/documents/Manuals/CommercialVehicle/TAVN111CDLDriverManual.pdf

http://www.aot.state.vt.us/dmv/documents/Manuals/DriverLicense/TAVN0072007DriverManual.pdf

Virginia

DMV website: http://www.dmv.state.va.us/

http://www.dmv.virginia.gov/webdoc/citizen/drivers/applyingcdl.asp

DMV website: http://www.dmv.state.va.us/

Washington

DMV website: http://www.dol.wa.gov/

http://www.dol.wa.gov/forms/520061.pdf

http://www.dol.wa.gov/driverslicense/driverguide.pdf

West Virginia

DMV website: http://www.wvdot.com/

http://www.wvdot.com/6_motorists/dmv/downloads/drivershandbook.pdf

http://www.wvdot.com/6_motorists/dmv/6g1a_licenseinfo.htm#Who%20Must%20Be%20Tested

http://www.wvdot.com/6_motorists/dmv/6g0_cdl.htm#Age%20&%20Fitness%20Requirements

Wisconsin

DMV website: http://www.dot.state.wi.us/

http://www.dot.wisconsin.gov/statepatrol/docs/trans112.pdf

http://www.dot.state.wi.us/drivers/docs/e-handbook.pdf

Wyoming

DMV website: http://www.dot.state.wy.us/

http://www.dot.state.wy.us/Default.jsp?sCode=drvcm

http://www.dot.state.wy.us/Default.jsp?sCode=drvvo

Appendix C: Study Retrieval Criteria

Retrieval Criteria for Studies included in Section 4: Narcolepsy and Crash Risk

- Article must have been published in the English language.
- Article must have enrolled 10 or more individuals.
- Article must describe a study that attempted to determine the risk for a motor vehicle crash directly (risk for crash) associated with narcolepsy or a study that attempted to evaluate the relationship between narcolepsy and the following direct and indirect measures of driver safety:
    - Crash
    - Measures of driving-related performance

Retrieval Criteria for Studies included in Section 5: Impact of Treatment of Narcolepsy on Driver Safety

- Article must have been published in the English language.
- Article must have enrolled 10 or more individuals.
- Article must describe a study that attempted to determine the risk for a motor vehicle crash associated with narcolepsy or a study that attempted to evaluate the relationship between narcolepsy and the following direct and indirect measures of driver safety:
    - Crash
    - Measures of driving-related performance
    - Cataplexy events
    - Measures of EDS
    - Measures of cognitive and psychomotor function

Appendix D: Study Inclusion Criteria

Inclusion Criteria for Studies included in Section 4: Narcolepsy and Crash Risk

- Article must have been published in the English language.
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more individuals.
- Article must have enrolled individuals aged ≥ 18.
- Article must describe a study that attempted to determine the risk for a motor vehicle crash associated with narcolepsy or a study that attempted to evaluate the relationship between narcolepsy and the following direct and indirect measures of driver safety:
    - Crash
    - Measures of driving-related performance
- Article may compare the proportion of drivers with narcolepsy who crashed with the proportion of comparable individuals without the disorder who did not crash.
- Article may compare the proportion of individuals with narcolepsy who crashed to those in the general population who experienced crash.
- Studies that evaluated both narcolepsy and other sleep disorders among individuals were included as long as the narcolepsy participants' data could be analyzed separately from that of other populations.
- If the same study is reported in multiple publications, the most complete publication will be the primary reference. Data will be extracted so as to avoid double-counting patients.
- Article must present motor vehicle crash risk data in a manner that will allow calculations (directly or through imputation) of effect size estimates and confidence intervals.
- Article must describe a dichotomous comparison between individuals with narcolepsy based on the outcome.

Inclusion Criteria for Studies Included in Section 5: Impact of Treatment of Narcolepsy on Driver Safety

- Article must have been published in the English language.
- Article must be a full-length article. Abstracts and letters to the editor will not meet this inclusion criterion.
- Article must have enrolled 10 or more individuals.
- Article must have enrolled individuals aged ≥ 18.
- Article must describe a study that attempted to determine the risk for a motor vehicle crash associated with narcolepsy or a study that attempted to evaluate the relationship between narcolepsy and the following direct and indirect measures of driver safety:
    - Crash
    - Measures of driving-related performance
    - Cataplexy events
    - Measures of EDS
    - Measures of cognitive and psychomotor function

Appendix E: Full-Length Articles Excluded

Table E-1: Excluded Studies (Section 4: Narcolepsy and Crash Risk)

Reference	Year	Reason for Exclusion
Powell et al.	2007	Narcolepsy not specifically examined
Frucht, Greene, & Fahn	2000	No crash data
Ferreira et al.	2000	Case study/no crash data
Phillip et al.	1996	Narcolepsy not specifically examined
Pakola, Einges, & Pack	1995	No crash data
Martikainen et al.	1992	Narcolepsy not specifically examined
Aldrich et al.	1986	No crash data
Broughton et al.	1983	Duplicate sample
Murray & Foley	1974	Review article
Grubb	1969	Letter to the editor
Kales et al.	1982	No crash data
Mitler et al.	1990	Review
Aldrich	1990	Review article
Broughton & Broughton	1994	No crash data
Goswami	1998	No crash data
Dodel et al.	2007	No crash data
Daniels et al.	2001	No crash data

Table E- 2: Excluded Studies (Section 5: Treatments for Narcolepsy on Driver Safety)

Reference	Year	Reason for Exclusion
Modafinil (Armodafinil)		
Schwartz et al.	2003	Single-arm pre-post study with no comparison group
Becker et al	2002	Single-arm pre-post study with no comparison group
Guilleminault et al.	2000	Single-arm pre-post study with no comparison group
Sodium Oxybate		
Huang et al.	2009	Study limited to teenage patients only
Husain et al.	2009	No relevant outcomes
Seeck, Hirschner et al.	2009	Case report (n=2)
Lammers et al.	1993	Examined the drug Gammahydroxybutyrate which is not FDA approved
Scrima et al.	1990	Examined the drug Gammahydroxybutyrate which is not FDA approved
Antidepressants		
Ristanovic et al.	2009	No relevant outcomes; examined the effect of withdrawal from antidepressants on cataplexy
Niederhoferet al.	2006	Case report (n=1)
Larrosa et al.	2001	Single-arm pre-post study with no comparison group
Thirumalai & Shubin	2000	Case report (n=3)
Hishikawa et al.	1966	Study prior to 1980
Chen et al.	1995	Lack of baseline characteristics

Reference	Year	Reason for Exclusion
Roselaar et al.	1987	No control group
Amphetamine		
Bruck et al.	2005	No relevant outcomes
Ivanenko et al.	2003	Study limited to children patients only
Parkes et al.	1975	Study prior to 1980
Yoss et al.	1959	Study prior to 1980
Daly et al.	1956	Study prior to 1980
Chen et al.	1995	Lack of baseline characteristics

Appendix F: Quality Assessment Instruments Used

Table F-1: Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies

Question #	Question
1	Are the exposed cohorts representative of the average motor vehicle driver in the community?
2	Are the nonexposed cohorts representative?
3	How was exposure determined – secure record?
4	At the designated start of the study, were the controls free of the outcome of interest?
5	What is the comparability of the cohorts on the basis of design or analysis?
6	How was the outcome assessed?
7	Was follow-up adequate for outcome to occur?
8	Was the follow-up adequate for both exposed and non-exposed cohorts?
9	Was the funding free of financial interest?
10	Were the conclusions supported by the data?

Table F-2: Quality Assessment Checklist for Parallel Group Controlled Trials

Question #	Question
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 the *characteristics* of patients in the different study groups comparable at the time they were assigned to groups?
5	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?
6	Was the comparison of interest prospectively planned?
7	Did ≥85% of the patients complete the study?
8	Was there a ≤15% difference in completion rates in the study's groups?
9	Was compliance with treatment measured?
10	Was compliance with treatment ≥85% in both of the study's groups?
11	Were all of the study's groups treated at the same center?
12	Were subjects blinded to the treatment they received?
13	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?
14	Did investigators use intent-to-treat in analyses?
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?
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?

Question #	Question
20	Was the instrument used to measure the outcome valid?
21	Were the follow-up times in all of the study's relevant groups approximately equal?
22	Was the funding for this study derived from a source that has financial interest in its results?
23	Were the author's conclusions, as stated in the abstract **or** the article's discussion sections, supported by the data?

Table F-3: Quality Assessment Checklist for Crossover Controlled Trials

Question #	Question
1	Were patients randomly assigned to the study's groups?
2	Did the study employ stochastic randomization?
3	Did subject return to initial state before beginning subsequent phases?
4	Was the comparison of interest prospectively planned?
5	Did ≥85% of the patients complete the study?
6	Was there a ≤15% difference in completion rates in the study's groups?
7	Was compliance with treatment measured?
8	Was compliance with treatment ≥85% in both of the study's groups?
9	Were all of the study's groups treated at the same center?
10	Were subjects blinded to the treatment they received?
11	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?
12	Did investigators use intent-to-treat in analyses?
13	Did analyses use methods specific to paired data (e.g., paired t-test, McNemar test)?
14	Was the treating physician blinded to the groups to which the patients were assigned?
15	Were those who assessed the patient's outcomes blinded to the group to which the patients were assigned?
16	Was there concealment of allocation?
17	Was the outcome measure of interest objective **and** was it objectively measured?
18	Were the same laboratory tests, clinical findings, psychological instruments, etc. used to measure the outcomes in all of the study's groups?
19	Was the instrument used to measure the outcome valid?
20	Were the follow-up times in all of the study's relevant groups approximately equal?
21	Was the funding for this study derived from a source that has financial interest in its results?
22	Were the author's conclusions, as stated in the abstract **or** the article's discussion sections, supported by the data?

Appendix G: Quality Score Tables

Table G-1: Quality Assessment Table for Evidence Base used in Section 4: Narcolepsy and Crash

Reference	Items										Quality Category
	1	2	3	4	5	6	7	8	9	10	
Crash Studies											
Aldrich, 1989	N	N	N	Y	N	N	Y	Y	NR	Y	Low
Broughton et al., 1981	N	N	N	Y	N	N	Y	Y	Y	Y	Low
Broughton, Guberman, & Roberts, 1984	N	N	N	Y	N	N	Y	Y	Y	Y	Low
Ozaki et al., 2008	N	N	N	Y	N	N	Y	Y	Y	Y	Low
Driving Performance Studies											
Findley et al., 1995	N	N	Y	Y	S	Y	Y	Y	Y	Y	Moderate
Findley, Suratt, & Dinges, 1999	N	S	Y	Y	N	Y	Y	Y	Y	Y	Moderate
George, Boudreau, & Smiley, 1996	N	S	Y	Y	Y	Y	Y	Y	Y	Y	Moderate
Kotterba et al., 2004	S	Y	Y	Y	N	Y	Y	Y	Y	Y	Moderate
Mitler, Hajdukovic, & Erman, 1993	N	N	Y	Y	S	Y	Y	Y	Y	Y	Moderate

N = No
NR = Not reported
S = Somewhat representative or partially validated
Y = Yes

Table G-2: Quality Assessment Table for Evidence Base Used in Section 5: Impact of Treatment

Reference	Items																						Quality Category
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	
Sodium Oxybate																								
Black & Houghton, 2006	Y	NR	N	Y	Y	Y	Y	Y	Y	NR	N	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
U.S. Xyrem Multicenter Study Group, 2002	Y	NR	N	Y	Y	Y	Y	NR	Y	NR	N	Y	N	N	Y	Y	Y	N	Y	UC	Y	Y	Y	High
Xyrem International Study Group, 2005	Y	NR	N	Y	Y	Y	Y	Y	Y	NR	N	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Modafinil																								
Harsh et al., 2006	Y	Y	N	Y	Y	Y	N	N	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Moderate
Joo et al., 2008	N	NA	N	Y	Y	Y	Y	Y	N	NA	NR	Y	N	NA	N	N	NR	Y	Y	Y	Y	N	Y	Low
Schwartz et al., 2003	Y	NR	N	N	N	Y	NR	NR	N	NA	N	Y	N	UC	Y	Y	Y	Y	Y	Y	Y	Y	Y	Moderate
Schwartz et al., 2004	Y	NR	N	Y	Y	Y	Y	Y	N	NA	Y	Y	N	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Thorpy et al., 2003	Y	NR	N	Y	Y	Y	Y	Y	N	NA	NR	N	NA	N	N	N	N	N	Y	UC	Y	Y	Y	Moderate
U.S. Modafinil in Narcolepsy Multicenter Group, 1998	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
U.S. Modafinil in Narcolepsy Multicenter Group, 2000	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Amphetamines																								
Mitler et al.,	N	NA	N	N	N	Y	UC	UC	N	NA	NR	N	N	NA	N	N	N	Y	Y	Y	Y	N	UC	Low

Reference	Items																						Quality Category
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	
1986																								
Antidepressants																								
Guilleminault et al., 1986	N	NA	N	NR	NR	Y	Y	Y	N	NA	N	Y	N	N	N	N	NR	Y	Y	Y	Y	NR	Y	Low
Lammers et al., 1991	Y	NR	N	NR	NR	Y	Y	Y	N	NA	NR	Y	N	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Mayer et al., 1995	Y	NR	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Mayer et al., 2003	Y	NR	N	Y	Y	Y	Y	Y	Y	NR	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Reinish et al., 1995	N	NA	Y	N	Y	Y	NR	NR	N	NA	NR	N	NA	N	N	N	N	Y	Y	Y	N	NR	Y	Low

N = No
NR = Not reported
UC = Unclear
Y = Yes
NA = Not applicable

Table G-3: Quality Assessment Table for Crossover Controlled Trials

Reference	Items																					Quality Category
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	
Modafinil																							
Boivin et al., 1993	Y	NR	Y	Y	Y	Y	N	NA	NR	Y	N	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Broughton et al., 1997	Y	NR	N*	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Saletu et al., 2004	Y	NR	Y	Y	Y	Y	N	NA	NR	Y	N	N	Y	Y	NR	NR	Y	Y	Y	Y	Y	Y	High
Saletu et al., 2009	Y	Y	Y	Y	Y	Y	N	NA	NR	Y	N	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Amphetamines																							
Mitler et al., 1993	Y	NR	Y	Y	Y	Y	N	NA	Y	Y	N	NA	Y	N	N	N	Y	Y	Y	Y	N	Y	Moderate
Shindler et al., 1985	N	N	N	Y	N	NR	N	NA	Y	N	NA	N	UC	N	N	N	N	Y	N	Y	Y	Y	Low
Antidepressants																							
Hublin et al., 1994	Y	NR	N	Y	Y	Y	N	NA	NR	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Schachter & Parkes, 1980	Y	NR	Y	Y	N†	N	N	NA	NR	N	NA	N	NA‡	N	N	NR	N	Y	UC – self report	Y	Y	Y	Moderate
Schrader et al., 1986	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	N	NA	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	High

N = No
NR = Not reported
UC = Unclear
Y = Yes
NA = Not applicable
*Carryover effects were minimized by using data from the second wk of each 2-wk period
† 50% of patients completed fluvoxamine phase and 100% completed clomipramine phase
‡ Only descriptive statistics provided

Appendix H: Sensitivity Analyses

Figure H- 1: Removal of Each Individual Study Separately from Meta-analysis of Narcolepsy and Crash Rate

Study name	Statistics with study removed				
	Point	Lower limit	Upper limit	Z-Value	p-Value
Aldrich, 1989	7.866	3.670	16.861	5.302	0.000
Broughton et al., 1981	5.545	2.575	11.936	4.378	0.000
Broughton et al., 1984	5.643	3.140	10.138	5.788	0.000
	6.146	3.504	10.781	6.334	0.000

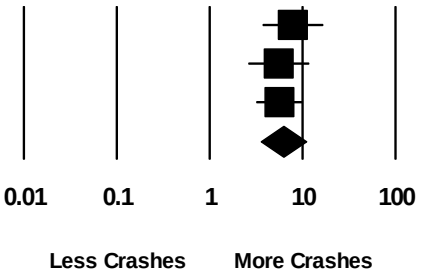

Figure H- 2: Removal of Each Individual Study Separately from Meta-analysis of Narcolepsy and Simulator Crash Rate

Study name	Statistics with study removed						
	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Findley et al., 1995	1.013	0.257	0.066	0.509	1.517	3.941	0.000
Findley et al., 1999	1.092	0.280	0.078	0.543	1.641	3.898	0.000
Kotterba et al., 2004	0.953	0.260	0.068	0.443	1.464	3.661	0.000
Mitler et al., 1993	0.950	0.248	0.061	0.464	1.436	3.832	0.000
	0.998	0.226	0.051	0.555	1.440	4.421	0.000

Appendix I: Recommended Protocols for MWT and MSLT

Recommendations for the MWT protocol

1. The 4-trial MWT 40-minute protocol is recommended. The MWT consists of four trials performed at two-hour intervals, with the first trial beginning about 1.5 to 3 hours after the patient's usual wake-up time. This usually equates to a first trial starting at 0900 or 1000 hours.
2. Performance of a polysomnogram (PSG) prior to MWT should be decided by the clinician based on clinical circumstances.
3. Based on the Rand/UCLA Appropriateness Method, no consensus was reached regarding the use of sleep logs prior to the MWT; there are instances, based on clinical judgment, when they may be indicated.
4. The room should be maximally insulated from external light. The light source should be positioned slightly behind the subject's head such that it is just out of his/her field of vision, and should deliver an illuminance of 0.10 to 0.13 lux at the corneal level (a 7.5 W night light can be used, placed 1 foot off the floor and 3 feet laterally removed from the subject's head). Room temperature should be set based on the patient's comfort level. The subject should be seated in bed, with the back and head supported by a bedrest (bolster pillow) such that the neck is not uncomfortably flexed or extended.
5. The use of tobacco, caffeine, and other medications by the patient before and during MWT should be addressed and decided upon by the sleep clinician before MWT. Drug screening may be indicated to ensure that sleepiness/wakefulness on the MWT is not influenced by substances other than medically prescribed drugs. Drug screening is usually performed on the morning of the MWT, but its timing and the circumstances of the testing may be modified by the clinician. A light breakfast is recommended at least 1 hour prior to the first trial, and a light lunch is recommended immediately after the termination of the second noon trial.
6. Sleep technologists who perform the MWT should be experienced in conducting the test.
7. The conventional recording montage for the MWT includes central EEG (C3-A2, C4-A1) and occipital (O1-A2, O2-A1) derivations, left and right eye EOGs, mental/submental EMG, and EKG.
8. Prior to each trial, the patient should be asked if they need to go to the bathroom or need other adjustments for comfort. Standard instructions for bio-calibrations (i.e., patient calibrations) prior to each trial include: (1) sit/lie quietly with your eyes open for 30 seconds, (2) close both eyes for 30 seconds, (3) without moving your head, look to the right, then left, then right, then left, right and then left, (4) blink eyes slowly for five times, and (5) clench or grit your teeth tightly together.
9. Instructions to the patient consist of the following: "Please sit still and remain awake for as long as possible. Look directly ahead of you, and do not look directly at the light." Patients are not allowed to use extraordinary measures to stay awake such as slapping the face or singing.
10. Sleep onset is defined as the first epoch of greater than 15 sec of cumulative sleep in a 30-sec epoch.

11. Trials are ended after 40 minutes if no sleep occurs, or after unequivocal sleep, defined as three consecutive epochs of stage 1 sleep, or one epoch of any other stage of sleep.
12. The following data should be recorded: start and stop times for each trial, sleep latency, total sleep time, stages of sleep achieved for each trial, and the mean sleep latency (the arithmetic mean of the four trials).
13. Events that represent deviation from standard protocol or conditions should be documented by the sleep technologist for review by the sleep specialist.

Recommendations for the MSLT Protocol

1. The MSLT consists of five nap opportunities performed at two-hour intervals. The initial nap opportunity begins 1.5 to 3 hours after termination of the nocturnal recording. A shorter four-nap test may be performed but this test is not reliable for the diagnosis of narcolepsy unless at least two sleep onset REM periods have occurred.
2. The MSLT must be performed immediately following polysomnography recorded during the individual's major sleep period. The use of MSLT to support a diagnosis of narcolepsy is suspect if total sleep time (TST) on the prior night sleep is less than six hours. The test should not be performed after a split-night sleep study (combination of diagnostic and therapeutic studies in a single night).
3. Sleep logs may be obtained for one week prior to the MSLT to assess sleep-wake schedules.
4. Standardization of test conditions is critical for obtaining valid results. Sleep rooms should be dark and quiet during testing. Room temperature should be set based on the patient's comfort level.
5. Stimulants, stimulant-like medications, and REM suppressing medications should ideally be stopped two weeks before MSLT. Use of the patient's other usual medications (e.g., antihypertensives, insulin, etc.) should be thoughtfully planned by the sleep clinician before MSLT testing so that undesired influences by the stimulating or sedating properties of the medications are minimized. Drug screening may be indicated to ensure that sleepiness on the MSLT is not pharmacologically induced. Drug screening is usually performed on the morning of the MSLT, but its timing and the circumstances of the testing may be modified by the clinician. Smoking should be stopped at least 30 minutes prior to each nap opportunity. Vigorous physical activity should be avoided during the day and any stimulating activities by the patient should end at least 15 minutes prior to each nap opportunity. The patient must abstain from any caffeinated beverages and avoid unusual exposures to bright sunlight. A light breakfast is recommended at least 1 hour prior to the first trial, and a light lunch is recommended immediately after the termination of the second noon trial.
6. Sleep technologists who perform MSLTs should be experienced in conducting the test.
7. The conventional recording montage for the MSLT includes central electroencephalogram (EEG) (C3-A2, C4-A1) and occipital (O1-A2, O2-A1) derivations, left and right eye electrooculograms (EOGs), mental/submental electromyogram (EMG), and electrocardiogram (EKG).
8. Prior to each nap opportunity, the patient should be asked if they need to go to the bathroom or need other adjustments for comfort. Standard instructions for bio-calibrations (i.e., patient

calibrations) prior to each nap include: (1) lie quietly with your eyes open for 30 seconds, (2) close both eyes for 30 seconds, (3) without moving your head, look to the right, then left, then right, then left, right and then left, (4) blink eyes slowly for five times, and (5) clench or grit your teeth tightly together.

9. With each nap opportunity the subject should be instructed as follows: "Please lie quietly, assume a comfortable position, keep your eyes closed, and try to fall asleep." The same instructions should be given prior to every test. Immediately after these instructions are given, bedroom lights are turned off, signaling the start of the test. Between naps, the patient should be out of bed and prevented from sleeping. This generally requires continuous observation by a laboratory staff member.
10. Sleep onset for the clinical MSLT is determined by the time from lights out to the first epoch of any stage of sleep, including stage 1 sleep. Sleep onset is defined as the first epoch of greater than 15 sec of cumulative sleep in a 30-sec epoch. The absence of sleep on a nap opportunity is recorded as a sleep latency of 20 minutes. This latency is included in the calculation of mean sleep latency (MSL). In order to assess for the occurrence of REM sleep, in the clinical MSLT the test continues for 15 minutes from after the first epoch of sleep. The duration of 15 minutes is determined by "clock time," and is not determined by a sleep time of 15 minutes. REM latency is taken as the time of the first epoch of sleep to the beginning of the first epoch of REM sleep regardless of the intervening stages of sleep or wakefulness.
11. A nap session is terminated after 20 minutes if sleep does not occur.
12. The MSLT report should include the start and end times of each nap or nap opportunity, latency from lights out to the first epoch of sleep, mean sleep latency (arithmetic mean of all naps or nap opportunities), and number of sleep-onset REM periods (defined as greater than 15 sec of REM sleep in a 30-sec epoch).
13. Events that represent deviation from standard protocol or conditions should be documented by the sleep technologist for review by the interpreting sleep clinician.