Evidence Report

Parkinson's Disease, Multiple Sclerosis, and Commercial Motor Vehicle Driver Safety (Comprehensive Review)

Presented to

The Federal Motor Carrier Safety Administration

June 3, 2009

Prepared for

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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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Table of Contents

Executive Summary

Purpose of Evidence Report

Of all occupations in the United States, workers in the trucking industry experience the third highest fatality rate, accounting for 12% of all worker deaths. About two-thirds of fatally injured truck workers were involved in highway crashes. According to statistics from the U.S. Department of Transportation (DOT), there were 4,932 fatal crashes involving a large truck in 2005 for a total of 5,212 fatalities. In addition, there were 137,144 nonfatal crashes; 59,405 of these were crashes that resulted in an injury to at least one individual (for a total of 89,681 injuries).

The purpose of this evidence report is to address several key questions posed by the Federal Motor Carrier Safety Administration (FMCSA). Each of these key questions was developed by the FMCSA such that the answers to these questions provided information that would be useful in updating its current medical examination guidelines. The five key questions addressed in this evidence report are as follows:

Key Question 1: What are the criteria that define when an individual with Parkinson's disease (PD) should stop driving a CMV?

Key Question 2: What is the impact of pharmacotherapy for PD on driver safety?

Key Question 3: Are individuals with multiple sclerosis (MS) at an increased risk for a motor vehicle crash? If so, what factors associated with MS are predictive of an increased crash risk?

Key Question 4: How frequently should individuals with MS be assessed in order to monitor whether they remain safe to drive?

Key Question 5: What is the impact of pharmacotherapy for MS on driver safety?

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.

A total of seven electronic databases (MEDLINE, PubMed (preMEDLINE), EMBASE, PSYCH Info, CINAHL, TRIS, the Cochrane library) were searched through April 23, 2008. 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 types of conclusion are 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. ECRI Institute recommends regular monitoring of the relevant literature for moderate-strength conclusions.
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. ECRI Institute recommends frequent monitoring of the relevant literature.
Insufficient	Although some evidence exists, the evidence is insufficient to warrant drawing an evidence-based conclusion. ECRI Institute recommends frequent monitoring of the relevant literature.
Quantitative Conclusion (Stability of Effect Size Estimate)	
High	The estimate of treatment effect in the conclusion is stable. It is highly unlikely that the magnitude of this estimate will change substantially as a result of the publication of new evidence.
Moderate	The estimate of treatment effect the conclusion is somewhat stable. There is a small chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI Institute recommends regular monitoring of the relevant literature.
Low	The estimate of treatment effect included in the conclusion is likely to be unstable. There is a reasonable chance that the magnitude of this estimate will change substantially as a result of the publication of new evidence. ECRI Institute recommends frequent monitoring of the relevant literature.
Unstable	Estimates of the treatment effect are too unstable to allow a quantitative conclusion to be drawn at this time. ECRI Institute recommends frequent monitoring of the relevant literature.

Evidence-Based Conclusions

Key Question 1: What criteria define when an individual with Parkinson's Disease (PD) should stop driving a CMV?

The evidence is insufficient to determine with precision what risk factors or combination of risk factors truly defines when an individual with PD should stop driving. However, potential risk factors

include movement restriction/decreased motor function, stage of PD, duration of PD, decreased cognitive function, and sudden onset of sleepiness (Strength of Evidence: Minimally Acceptable).

Direct Evidence – Crash Studies: Three studies in non-commercial motor vehicle (non-CMV) driver populations provided direct evidence to address this question. One low-quality cohort study found that subgroups of patients with Hoehn and Yahr stages 2 and 3 showed a significantly increased crash risk compared to control individuals without PD ($p = 0.001$, $p = 0.008$). No evidence of increased crash risk was found among patients in Hoehn and Yahr Stage 1. A low-quality cohort study evaluating outcomes in driving patterns among individuals with PD found that individuals with movement restriction had a significantly increased crash risk compared to individuals without movement restriction ($p = 0.034$). One low-quality survey study evaluating outcomes of sudden onset of sleepiness and driving behavior found that disease severity, sleepiness, and driving exposure showed a significant association with crash prediction. However, these findings need to be replicated before a definitive conclusion can be reached. Limitations of the evidence supporting this conclusion are the small size of the evidence base (three studies) and overall low quality.

Indirect Evidence – Studies of Driving Tests and Driving Simulation: Twelve cohort studies (nine moderate-quality, three low-quality) evaluated outcomes indirectly associated with crash risk among non-CMV drivers with PD. One study showed a significant association of ESS scores and Inappropriate Sleep Composite Scores with risk of falling asleep while driving ($p < 0.001$). Three studies' multivariate assessment of driving fitness showed a significant difference in factors (disease duration, contrast sensitivity, cognitive function, and motor function) associated with PD individuals who failed a driving assessment compared to individuals passing a driving assessment. However, predicting which individuals will pass or fail a driving assessment is not the same as predicting which individuals who pass a driving assessment will have an increased crash risk. Whether the variables identified in these studies can predict which patients with PD who pass a driving assessment are at increased risk of crash remains to be determined. Another study identified disease stage, car test score, and reaction time to brake as predictors of driving suitability using stepwise discriminant analysis.

Of the remaining studies, three studies that shared most of the same patients used multivariate analyses and identified various neuropsychological measures as predictors of at-fault safety errors and incorrect turns during on-road testing. No significant association was found with daily levodopa dosage or type of medication and driving performance outcomes. Another study used stepwise regression to determine that slowness of visual processing, levodopa dosage, and age explained 67% of the variation in faults and offenses in the on-road driving test for drivers with PD. Disease indices (Hoehn and Yahr scale, duration of disease, and mini-mental state exam [MMSE] scale) did not show significant correlation with driving results in this study.

The three remaining studies evaluated factors associated with simulated driving outcomes. One study found that a significant increase in simulator crash correlated with increasing Hoehn and Yahr stage ($p = 0.006$). The other two studies identified various neuropsychological measures as variables correlating with performance measures on a driving simulator. However, the possibility exists that some of these

variables might not have remained significantly correlated with driving performance had a multivariate analysis been performed.

The findings of studies that used multivariate assessment or discriminant function analysis for predicting driving performance should be given greater consideration than the studies that did not as these studies attempt to isolate the true predictability of the associated risk factors evaluated within the studies. Also, studies that evaluated driving performance on the road should be given greater consideration than studies that evaluated driving performance on a simulator.

We were not able to assess the crash risk for PD among CMV drivers. The lack of studies enrolling CMV drivers with PD precludes one from determining whether CMV drivers with this condition are at an increased risk for a motor vehicle crash.

Key Question 2: What is the impact of pharmacotherapy for PD on driver safety?

Evidence suggests that use of dopamine agonists may lead to somnolence (sleepiness) in individuals with PD. (Strength of Evidence: Moderate) The evidence is insufficient to determine whether other types of pharmacotherapy may affect driver safety. Whether measures of somnolence among individuals with PD taking pharmacotherapy can predict actual crash risk cannot be determined from currently available evidence.

Direct Evidence – Crash Studies: No included studies provided direct evidence of crash risk with noncommercial drivers.

Indirect Evidence – Studies of Driving Performance: The four included studies (ranging from moderate to high quality) evaluated the effect of dopamine agonists on an indirect outcome (sleepiness) which may be associated with driver safety. The combined data from two randomized controlled trials (RCTs) found that individuals with PD given pramipexole tend to be at an increased risk of somnolence compared to those given placebo ($p = 0.002$). Another RCT found a large and significant increase in risk of somnolence among patients using ropinirole compared to patients given placebo ($p < 0.0001$). The results of a meta-analysis combining the three RCTs showed a statistically significant and robust risk of somnolence among patients with PD treated with dopamine agonists ($p = 0.006$).

We were not able to assess the impact of pharmacotherapy for PD on driver safety among CMV drivers. The paucity of data from studies enrolling CMV drivers treated with PD pharmacotherapy precludes one from determining whether CMV drivers with this type of condition are at an increased risk for a motor vehicle crash.

Key Question 3: Are individuals with Multiple Sclerosis (MS) at an increased risk of motor vehicle crash? If so, what factors associated with MS are predictive of an increased crash risk?

Currently available evidence suggests that some drivers with MS may have an elevated risk of crash compared to drivers without MS. (Strength of Evidence: Minimally Acceptable) Preliminary evidence suggests that crash risk may be increased predominantly among a subgroup of individuals with MS

and cognitive impairment, while individuals with MS but no cognitive impairment may not have an increased crash risk. However, more evidence is needed for a definitive conclusion concerning the effect of other factors on crash risk among drivers with MS.

Direct Evidence: Two moderate-quality cohort studies evaluated outcomes directly associated with crash risk among non-CMV drivers with MS. Although the summary effect size in both studies suggested increased crash risk among drivers with MS, the findings did not reach statistical significance in either study. However, a pooled analysis of data from both studies found statistically significant elevated odds of crash among drivers with MS compared to drivers without MS.

In one of these studies a subgroup of MS patients with cognitive impairment showed significantly increased crash risk compared to control individuals without MS, whereas a subgroup of MS patients without cognitive impairment did not show significantly increased crash risk compared to controls. The individuals in this study had minimal or no physical limitations, so they were not in a severe stage of MS. This finding suggests that cognitive impairment caused by MS may be a more important predictor of crash risk than simply having MS. However, this finding needs to be replicated before a definitive conclusion can be reached concerning the effect of other factors on crash risk among drivers with MS.

Indirect Evidence – Road Test and Driving Simulator Studies: Two moderate quality cohort studies evaluated outcomes that may be indirectly associated with crash risk among non-CMV drivers with MS. One study found that MS drivers who failed a road test scored significantly worse ($p < 0.05$) on six out of 23 cognitive tests compared to MS drivers who passed a road test. This study included patients with a wide spectrum of disease severity, ranging from independent mobility to wheelchair dependence. In the other study, assessment of useful-field-of-view (UFOV) performance related to simulated driving showed that a subgroup of MS patients with cognitive impairment had a significant increase in estimated crash risk ($p < 0.01$) compared to control individuals without MS, whereas a subgroup of MS patients without cognitive impairment did not show a significant increase in estimated crash risk compared to the control group. Assessment of neurocognitive driving performance within the same study showed a significant increase in latency time scores for MS patients with cognitive impairment compared to MS patients without cognitive impairment and healthy controls. The errors subcategory did not show a significant difference among these three groups. The patients in this study had minimal or no physical limitations. Whether these findings have any relationship with actual crash risk remains uncertain. Limitations of this evidence include small sample size (two studies) and moderate study quality.

We were not able to assess the crash risk for MS among CMV drivers. The lack of studies enrolling CMV drivers with MS precludes one from determining whether CMV drivers with this condition are at an increased risk for a motor vehicle crash.

Key Question 4: How frequently should an individual with MS be assessed in order to monitor whether they remain safe to drive?

No evidence was identified regarding assessment time interval for monitoring driver safety in patients with MS. Therefore, no evidence-based conclusion is possible at the present time.

Our searches identified no potentially relevant articles that addressed this question.

Key Question 5: What is the impact of pharmacotherapy for MS on driver safety?

No evidence was identified concerning the relationship between MS pharmacotherapy and driver safety outcomes. Therefore, no evidence-based conclusion is possible at the present time.

Our searches identified no potentially relevant articles that addressed this question.

Preface

Organization of Report

This evidence report contains four major sections: 1) *Background*, 2) *Parkinson's Disease, Multiple Sclerosis, and Driving Regulations*, 3) *Methods*, and 4) *Evidence Synthesis*. These major sections are supplemented by extensive use of appendices.

The *Background* section summarizes basic information on Parkinson's disease (PD) and multiple sclerosis (MS). In the section titled *Parkinson's Disease, Multiple Sclerosis, and Driving 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%) in the United States. About two-thirds of fatally injured truck workers were involved in highway crashes. According to the U.S. Department of Transportation (DOT), there were 137,144 non-fatal crashes involving a large truck in 2005. 59,405 of those crashes resulted in an injury to at least one individual, for a total of 89,681 injuries. 4,932 of all crashes caused 5,215 fatalities. In 2006, DOT's *Brief Statistical Summary* reported a total of 805 motorists killed in large truck crashes, which amounted to an increase of 0.1% over the statistics for 2005 (n = 804). The total number of motorists injured in large truck crashes was 23,000, which represented a decrease of 15% when compared to 2005 figures (n = 27,000).(1)

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

Key Question 1: What are the criteria that define when an individual with Parkinson's disease should stop driving a CMV?

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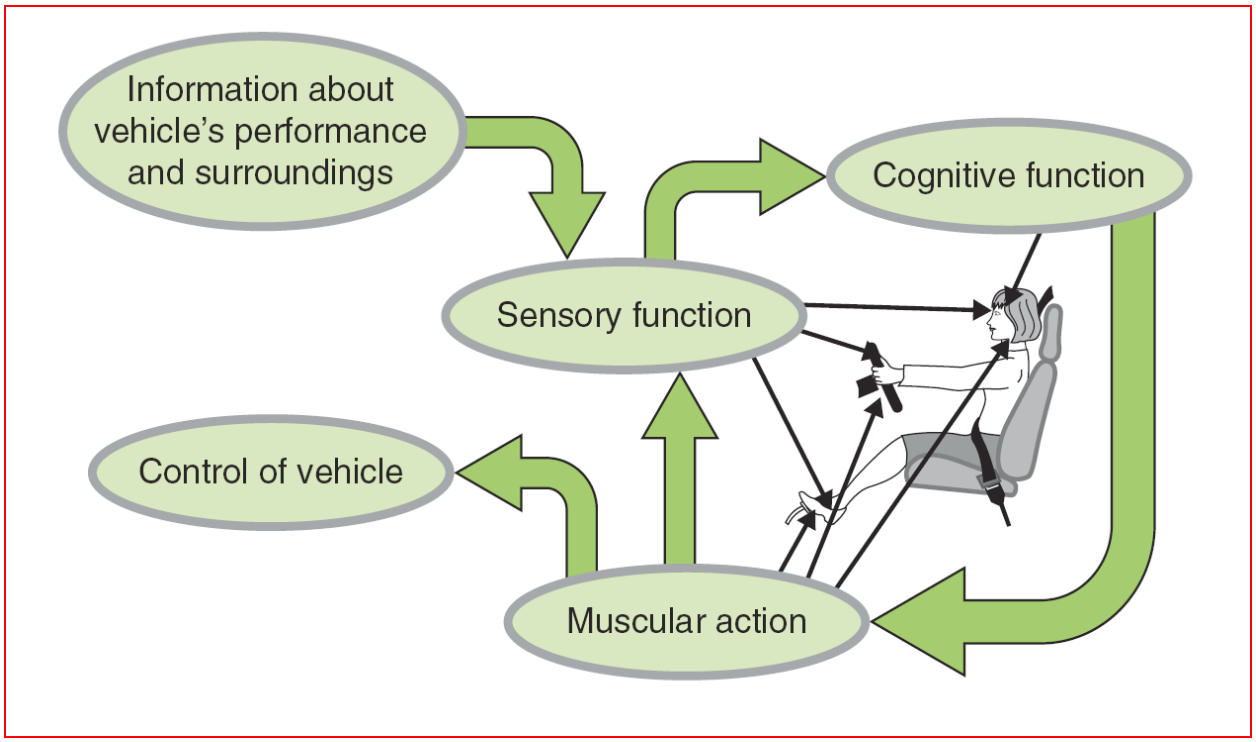
Background

Safe driving requires the driver to be able to maintain effective and reliable control of his or her vehicle; the capacity to respond to the road, traffic, and other external clues; and be able to follow the "rules of the road." Drivers consciously learn all these skills and demonstrate them as part of obtaining their commercial drivers license (CDL); the vast majority of people have the ability to achieve a satisfactory standard. Driving performance generally improves with experience, and driving ultimately becomes an "overlearned" skill that is subconsciously retained and can readily be used as required. Impairments caused by health problems can interfere with driving performance.

The purpose of this evidence report is to summarize the available data pertaining to the relationship between PD or MS and CMV driver safety. Driving is a complicated psychomotor performance, which depends on fine coordination between the sensory and motor systems. It is influenced by factors such as arousal, perception, learning, memory, attention, concentration, emotion, reflex speed, time estimation, auditory and visual functions, decision making, and personality. Complex feedback systems interact to produce the appropriate coordinated behavioral response (Figure 1). Anything that interferes with any of these factors to a significant degree may impair driving ability.(2) Cerebrovascular events such as stroke have the potential to impair cognitive and motor skills that are required for safe driving.

Figure 1. The Driving Task



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

Multiple Sclerosis (MS)

MS is a degenerative disease of the central nervous system. The signs and symptoms of the disease are thought to be a consequence of the destruction of the myelin sheath (demyelination) that insulates the axons in the brain and spinal cord (Figure 2). As the myelin sheath is destroyed, it is replaced by hard sclerotic plaques that result in distortions or complete abolition of nerve impulses.(3-5) Figure 3 shows magnetic resonance imaging (MRI) of a brain of a person with MS in which there are white lesions in the white matter caused by damage to myelin sheaths.(6)

Figure 2. Neurons with Normal and Damaged Myelin Sheaths(7)

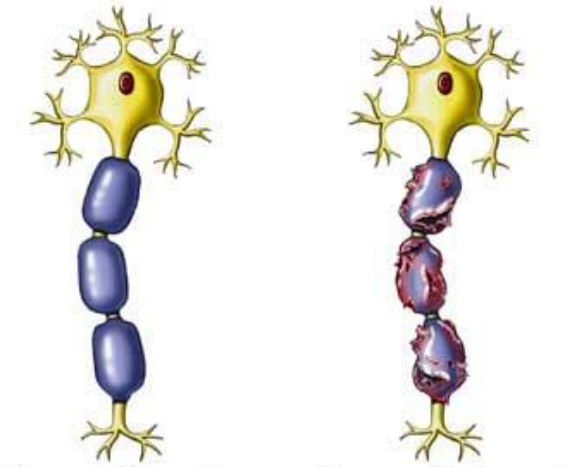
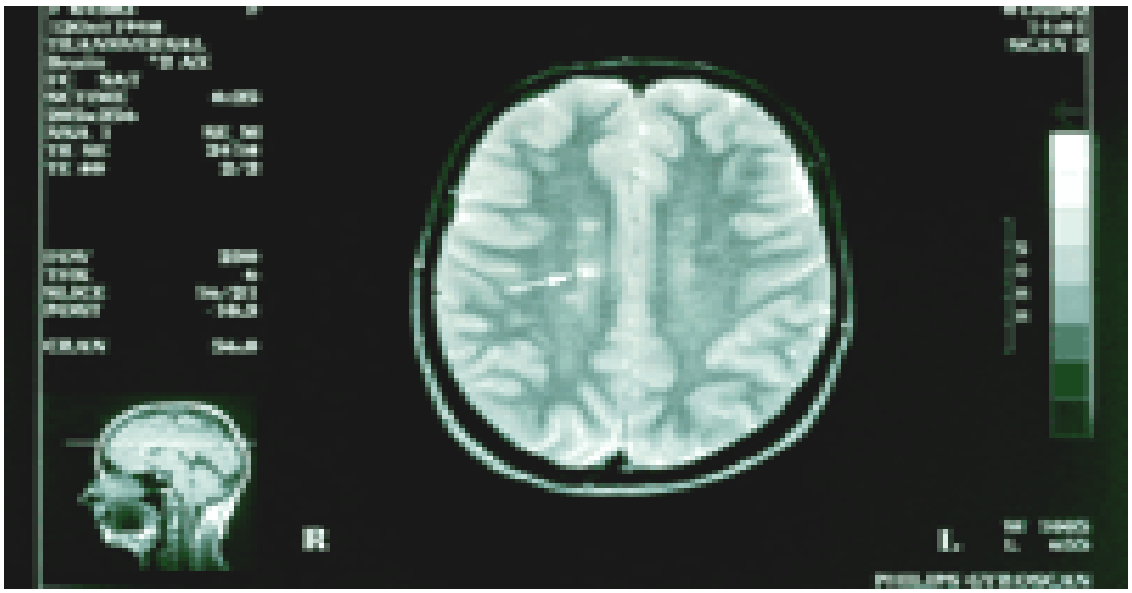


Figure 3. MRI of an MS Patient(6)



There are five main types of MS: (a) benign MS; (b) relapse remitting MS; (c) primary progressive MS; (d) secondary progressive MS; and (e) progressive relapsing MS. Patients with a first attack of MS, called a clinically isolated syndrome, generally have a second attack within five years of the initial attack and usually within the first two years of the initial attack.(6) MS types and characteristics are presented in Table 2.(6,8-11)

Table 2. Types of Multiple Sclerosis

Type	Prevalence	Characteristics
Benign MS	25% of MS patients and 15% of relapse remitting patients	Mild course with minimal disability. May not have symptoms for at least 10 years. Symptoms are mild to moderate and do not get worse or cause permanent disability. There is no method of determining who has benign MS. So, many people diagnosed with MS may be taking medication they don't yet need and suffering from unnecessary anxiety. Drugs are useful but are not always necessary.
Relapse Remitting MS (RRMS)	85% of MS patients	Patient has episodic relapses and remissions that might be partial or complete. First attack is called a clinically isolated syndrome. Symptoms suddenly reappear every few years, last for a few weeks or months, and then go back into remission. Symptoms sometimes worsen with each occurrence. Drugs are useful.
Primary Progressive MS (PPMS)	10-15% of MS patients	Slowly progressive pattern without relapses and remissions. Symptoms gradually worsen after symptoms first appear. Drugs not useful.
Secondary Progressive MS (SPMS)	50% of RRMS in 10 yrs & 90% of RRMS in 25 yrs.	Secondary progressive MS is a phase of progression with or without attacks. After time, even years, without relapses and remissions, patients may later relapse. Symptoms suddenly begin to progressively worsen. Drugs are not useful.
Progressive Relapsing MS	5% of PPMS patients	Least common form of MS. After time without relapses, patients relapse. Symptoms gradually worsen after symptoms first appear. One or more relapses may also occur. Drugs are not useful.

Diagnosis and Screening

The diagnosis of MS involves a thorough history and physical examination and results of diagnostic tests such as MRI of the brain, spinal tap to examine spinal fluids, and evoked potentials to measure how quickly and accurately a person's nervous system responds to certain stimulation. There is no single test for detecting MS. Several tests must be done and compared. Symptoms of MS include tingling, numbness, slurred speech, blurred or double vision, muscle weakness, poor coordination, unusual fatigue, muscle cramps, bowel and bladder problems, and paralysis.(3-5)

Since the 1980's, the Poser criteria was used to classify MS, which involved classifying evidence from two episodes of MS and identifying the involvement of white matter in more than one site in the central nervous system.(6,7,12) Currently, the McDonald criteria is the accepted classification system for MS that incorporates clinical and laboratory elements and allows for an earlier confirmation of the diagnosis. With both the Poser and McDonald criteria, MS is diagnosed based on two MS episodes

involving two or more areas of the central nervous system. However, the McDonald criteria additionally include MRI to show where multiple areas of involvement are and when new lesions appear.(6,7,12)

Life spans are six years shorter than for people without the disease. Most people with MS have a relatively normal life span and life expectancy is about 35 years after onset. After 25 years, approximately two-thirds of patients remain mobile. The disorder eventually results in physical limitations in about 70% of patients.(3,5,13)

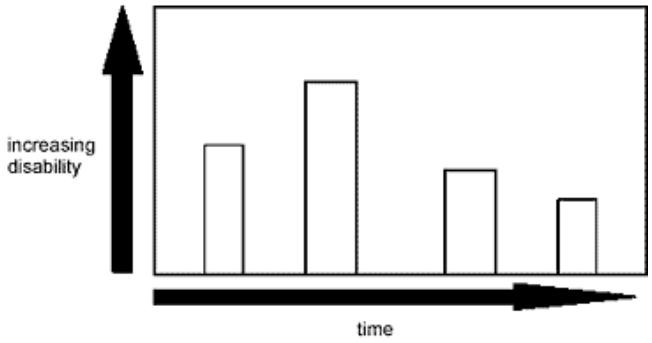
Course of Disease

MS usually appears in young adulthood. Symptoms appear most often between ages 20 and 35 to 40.(3,5) However, evidence suggests that MS is present long before the first symptom appears.(6) The major problem associated with the disease is lost mobility. Symptoms can include: numbness, muscle weakness, uncontrollable tremors, slurred speech, loss of bladder and bowel control, memory lapses, paralysis, and wild mood swings (from depression to euphoria). MS affects numerous (multiple) parts of the nervous system and is often characterized by periods of partial and sometimes complete recovery. MS is not fatal in and of itself, but it weakens the person and makes the person more susceptible to infections.(3,5,13)

The National Multiple Sclerosis Society has mapped the relationship between time and severity of disability for four courses of MS. These relationships are indicated in Figure 4 through Figure 7. Relapse remitting MS is characterized by clearly defined acute attacks with full recovery or with residual deficit upon recovery (Figure 4). Primary progressive MS is characterized by progression of disability from onset, without plateaus or remissions or with occasional plateaus and temporary minor improvements (Figure 5). Secondary progressive MS begins with an initial relapsing-remitting disease course, followed by progression of disability that may include occasional relapses and minor remissions and plateaus (Figure 6). Progressive elapsing MS shows progression of disability from onset but with clear acute relapses, with or without full recovery (Figure 7).(11)

Figure 4. Relapse Remitting MS (RRMS)

a) Acute attacks with full recovery



b) Acute attacks with residual deficits

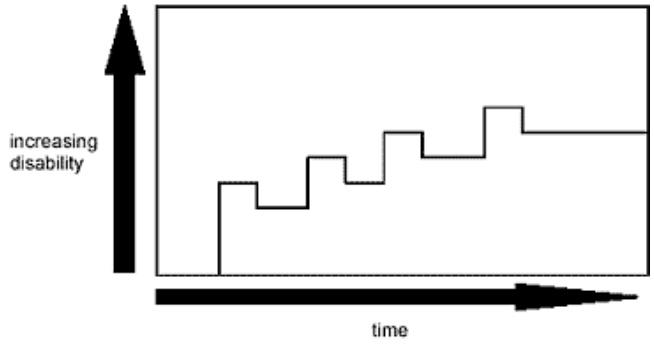
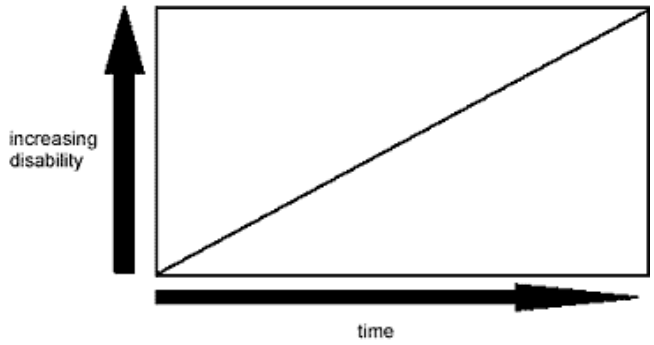


Figure 5. Primary Progressive MS (PPMS)

a) Progression of disability from onset without plateaus or remissions



b) Progression of disability from onset with occasional plateaus and temporary minor improvements

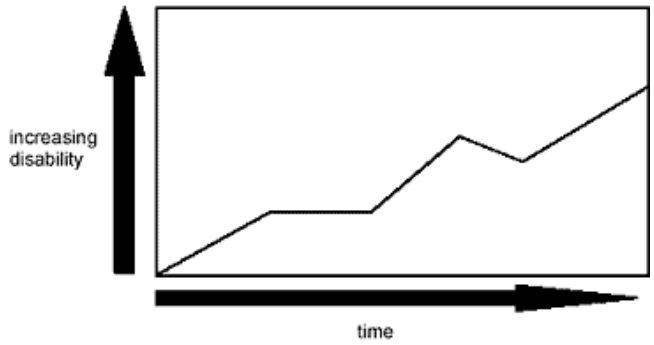
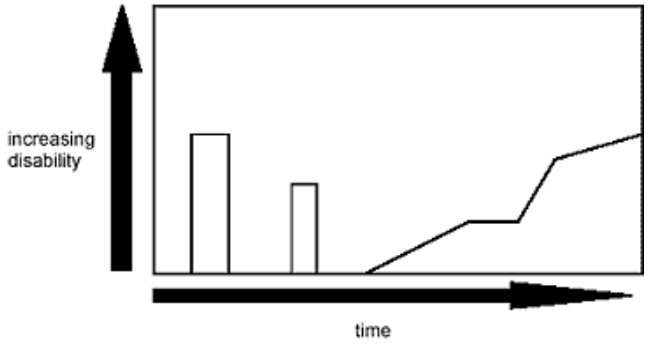


Figure 6. Secondary Progressive (SPMS)

a) Initial relapsing-remitting disease course followed by progression of disability



b) Initial relapsing-remitting disease course followed by occasional relapses and minor remissions and plateaus

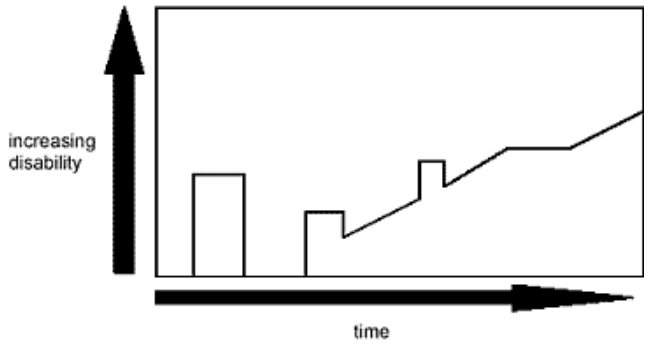
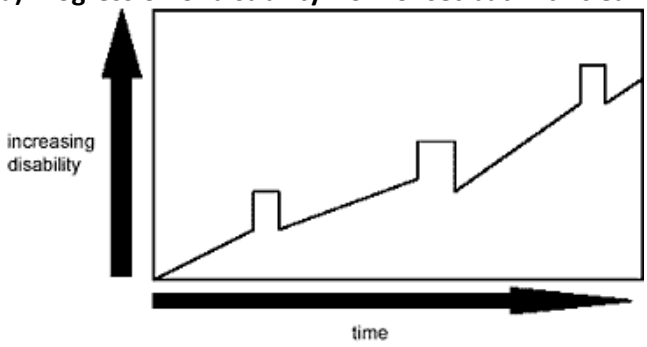
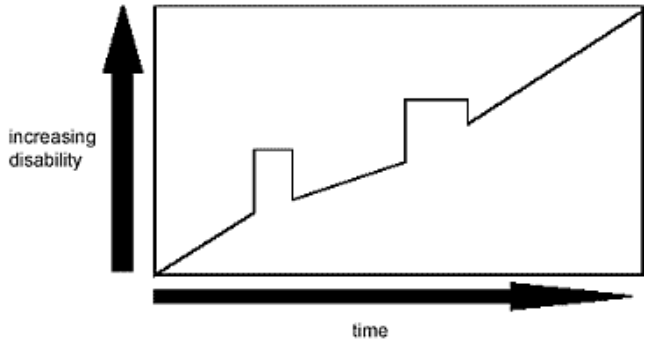


Figure 7. Progressive Relapsing Multiple Sclerosis (PRMS)

a) Progression of disability from onset but with clear acute relapses with full recovery



b) Progression of disability from onset but with clear acute relapses without full recovery



MS disease progression is typically monitored in four ways: 1) Radiographically—by looking for new lesions, gadolinium-enhanced lesions, or an increased amount of disease on MRI, 2) Electrophysiologically—by measuring changes in the sensory evoked potentials, 3) Neurologically—by measuring changes in function on the neurologic examination, and 4) Functionally—by assessing the person's physical and cognitive abilities.(11) In addition, a number of neurological rating scales are available to help physicians measure and quantify disability, impairment, and disability. These instruments include: (a) Scripps scale (or Neurological Rating Scale from the Scripps Clinic)(14); (b) ISS (Illness Severity Scale)(15); (c) The Krupp Fatigue Severity Scale (FSS)(16); (d) The Incapacity Status Scale (ISS)(16); (e) The Functional Independence Measure (FIM)(16); (f) The Ambulation Index (AI)(16); (g) The Functional Assessment of Multiple Sclerosis (FAMS)(16); (h) Profile of Mood States (POMS); (i) Sickness Impact Profile (SIP)(16); the CAMBS (Cambridge Multiple Sclerosis Basic Score)(17); and (j) Expanded Disability Status Scale (EDSS).(18) While the Scripps Neurologic Rating Scale and the FSS are widely recognized,(16) the EDSS is the most commonly used instrument for measuring impairment in individuals with MS today and is a standard measurement instrument in clinical practice and in trials.(16,19) All of the scales have pros and cons with regard to psychometric properties.(20)

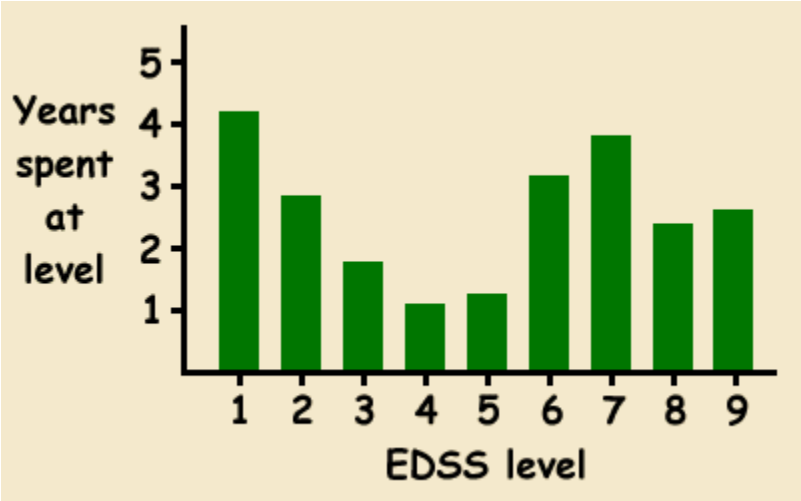
A copy of the EDSS appears in Table 3. Using the EDSS, patients are rated and given a score in each of eight Functional Systems. The Functional Systems include pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and an "other" category. EDSS steps 1.0 to 4.5 refer to people with MS who are fully ambulatory. EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation.(18) The average time a person spends in each EDSS level is presented in Figure 8.(16)

Table 3. Kurtzke Expanded Disability Status Scale (EDSS)

Kurtzke Expanded Disability Status Scale(18)	
0.0	Normal neurological examination
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. Fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS and more than minimal disability in several others
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest about 500 meters
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability; able to walk without aid or rest about 300 meters
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (work a full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting
7.0	Unable to walk beyond approximately five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair about 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of day; has some effective use of arms retains some self care functions
9.0	Confined to bed; can still communicate and eat
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

FS = Functional systems.

Figure 8. The average time an individual spends at each Kurtzke EDSS level(16)



In summary, the degree of disability varies among individuals with MS. According to a 2-year population based follow-up study,(21) one of three individuals will still be able to work after 15–20 years. Fifteen percent of people diagnosed with MS never have a second relapse, and these people have minimal or no disability after 10 years. The degree of disability after 5 years correlates well with the degree of disability after 15 years. This means that two-thirds of people with MS with low disability after 5 years will not get much worse during the next 10 years. These outcomes were observed before the use of medications such as interferon, which can delay disease progression for several years.(21)

Prevalence and Incidence

MS is the most common disabling neurological disease in young adults.(6) There is considerable variation in the occurrence of MS around the world. The prevalence of MS worldwide is approximately 2.5 million cases.(22) Based on 2008 data from the World Health Organization (WHO) and the Multiple Sclerosis International Federation (MSIF), the distribution of MS cases worldwide (prevalence) is presented in Figure 9, and the distribution of new cases worldwide (incidence) is presented in Figure 10.

Figure 9. 2008 Prevalence of MS Globally(23)

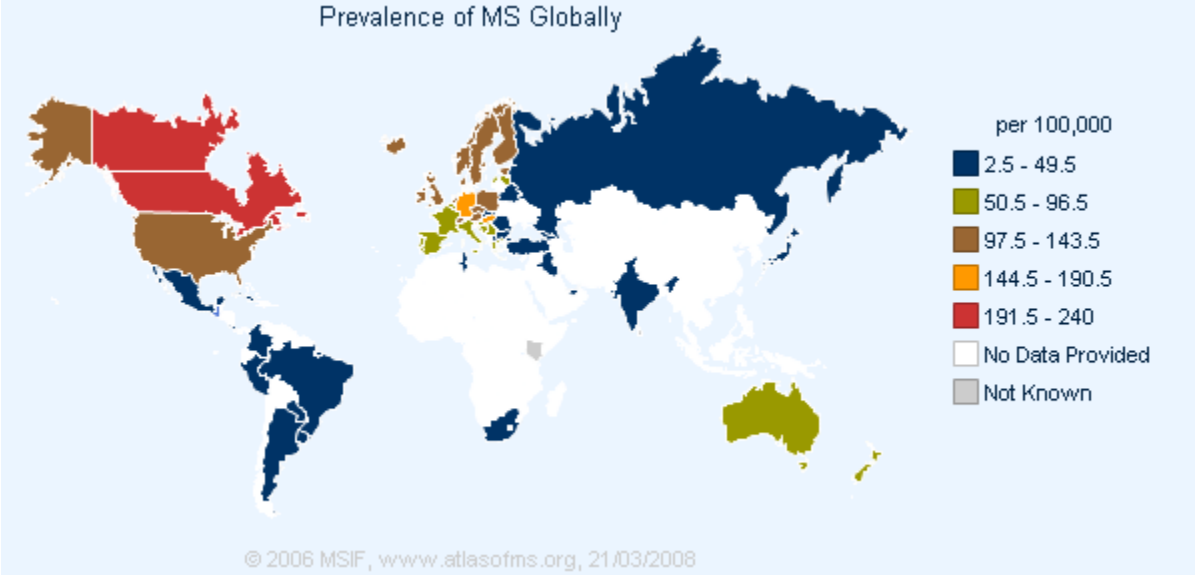
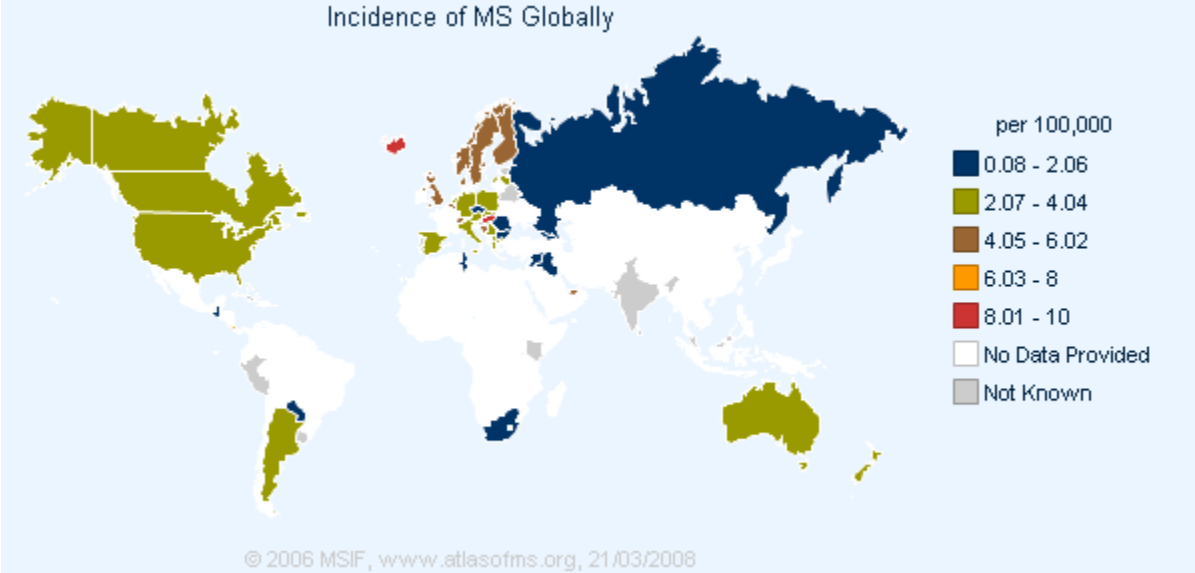


Figure 10. 2008 Incidence of MS Globally(23)



Based on 2008 data from WHO and MSIF MS Atlas Data,(23) the prevalence and incidence of MS in North America are presented in Figure 11 and Figure 12 respectively.

Figure 11. 2008 Prevalence of MS in North America(23)

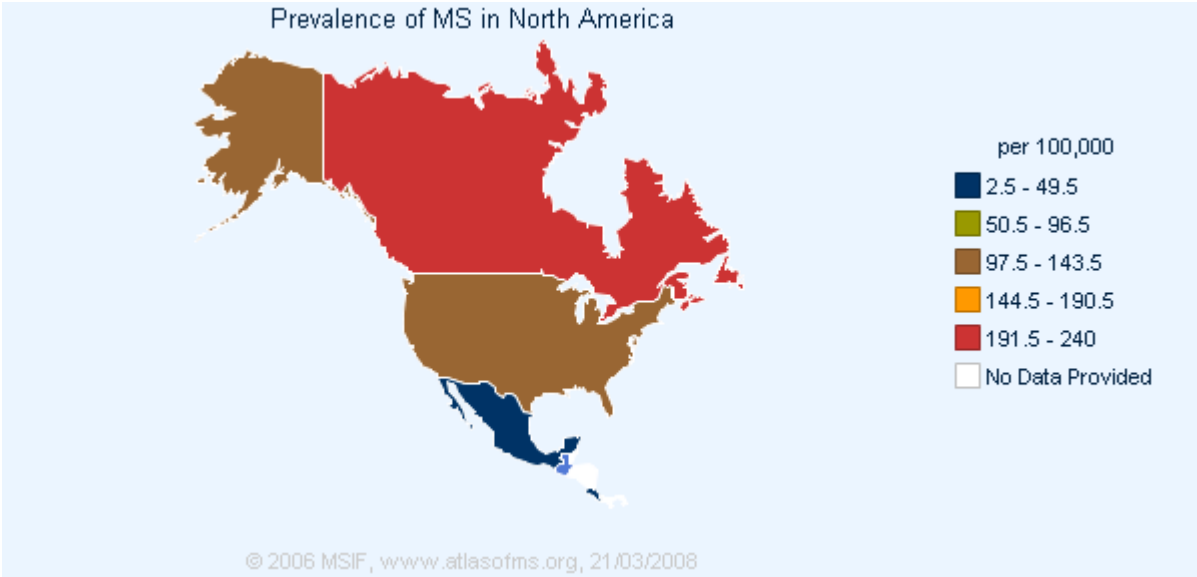
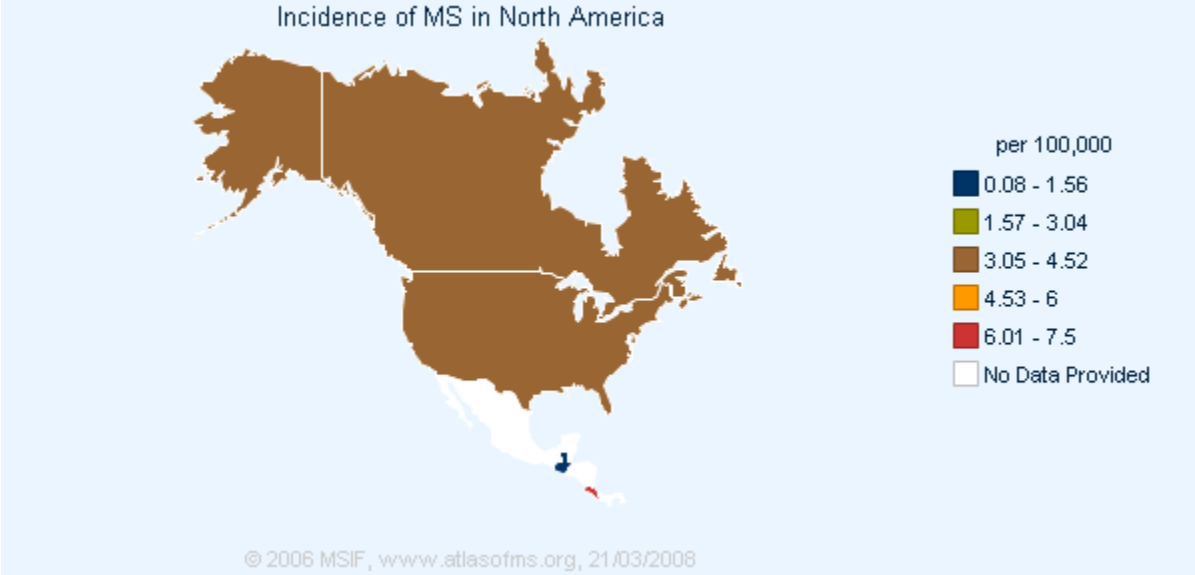
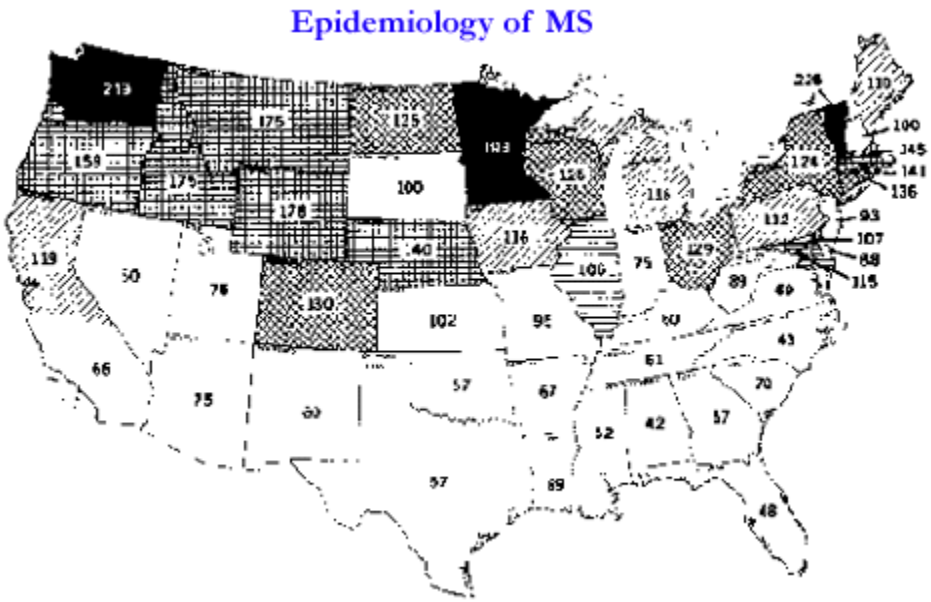


Figure 12. 2008 Incidence of MS in North America(23)



According to the National Institute of Neurological Disorders and Stroke, about 250,000 to 350,000 people in the United States have MS;(5) however, estimates from WHO and MSIF estimate that about 320,032 to 400,000 people in the United States have MS.(23) In early 2006, the National Multiple Sclerosis Society estimated that four hundred thousand people were diagnosed with MS in the United States and that two hundred people are newly diagnosed with MS every week.(9) As indicated in Figure 13 below, the prevalence of MS was about twice as high in North Dakota than it was in Florida in 2006.

Figure 13. 2006 Prevalence of MS (cases/100,000) in the United States(9,24,25)



MS is approximately twice as common in women as in men, and recent data suggest that the prevalence among women is increasing, as indicated in Figure 14.(26) In 2008, based on the MS Atlas project, WHO and MSIF estimate that one male to every three females have MS.(23) Similar trends have been found in other studies: more males than females have MS, and increasingly more women seem to be getting MS. As indicated in Table 4,(23) more women than men have MS, which holds true for every age group; MS is more prevalent in Caucasians than in African Americans and in any other races in the USA; and it is rare among African Americans and Native Americans. The greatest number of people with MS seems to be in the 30- to 69-year age groups, with the greatest number of men in the 50- to 59-age range and the greatest number of women in the 40- to 49-age range. The mean onset of MS in the United States seems to be between 30 and 39 years of age.(23) Within the United States, most cases of MS are in the northern rather than southern states. Worldwide, MS is thought by some to occur more frequently in higher altitudes than in places closer to the equator, in both northern and southern hemispheres.(24,25) There seem to be no data on prevalence of MS in CMV drivers.

Several authors have noted the difficulties in diagnosing and identifying MS and in accurately deriving prevalence and incidence estimates for MS.(26-28) As stated by Poser and Brinar,(28) "Review of the recent medical literature raises doubts about the reliability of reported prevalence rates of multiple sclerosis (MS). Many published prevalence rates are inflated. Some studies have shown that relying on clinical information and MRI interpretation leads to one third of incorrect MS diagnoses. The most important error is failing to distinguish between the clinical and MRI characteristics of MS and of disseminated encephalomyelitis (DEM) in both their acute and relapsing forms. The diagnostic criteria in current usage, including those relating to imaging, do not differentiate between MS and other recurrent inflammatory demyelinating diseases of the central nervous system. Considering a second demyelinating episode following a clinically isolated symptom or acute DEM, as confirming MS, is another major source of error. Another is including cases with onset before they entered the study group or moved to the geographic area. Neuromyelitis optica (NMO) has long been considered an MS variant and in Far Eastern countries it is counted as the 'oriental' form of MS, falsely inflating prevalence rates of MS in those areas. Recent immunologic and radiologic evidence shows that at least some NMO cases represent instances of DEM."(28)

Figure 14. Estimated number of persons (per 100,000 civilian, non-institutionalized U.S. population) reporting multiple sclerosis as a cause for limitation of activity, National Health Interview Survey, 1982-1996(26)

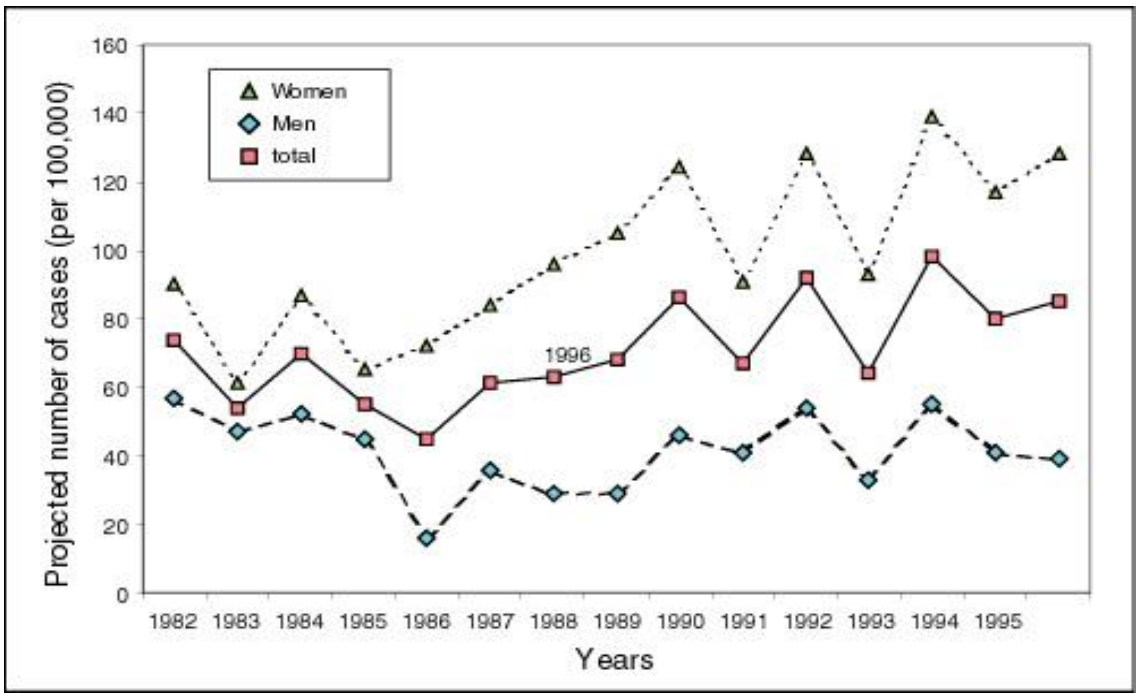


Table 4. MS in the United States by gender, age, and ethnicity/race(23)

Variable	Men	Women	Total
Race/ethnicity			
White	54 ± 4 1	37 ± 8	96 ± 5
Black/African America	25 ± 8*	68 ± 15	48 ± 9
All other races/ethnicities	19 ± 10*	67 ± 19	43 ± 11
Age group, y <30	5 ± 2*	25 ± 5	15 ± 2
30-39	58 ± 11	145 ± 17	102 ± 11
40-49	110 ± 17	305 ± 27	209 ± 16
50-59	123 ± 20	237 ± 26	182 ± 16
60-69	98 ± 18	190 ± 26	148 ± 17
70 +	33 ± 12*	105 ± 19	76 ± 12
Total	48 ± 4	123 ± 7	87 ± 4†

Estimated number of people (per 100,000 civilian, noninstitutionalized U.S. population) with MS by age, race/ethnicity, and sex, based on the National Health Interview Survey, 1989 through 1994. Values are expressed as estimated number of people ±SEM.

*Estimate is unstable. Standard error/estimate >0.3.

† This overall estimate differs slightly from the prevalence estimate of 85/100,000 presented in the text, because the table data is based on all reports of MS among those surveyed, not only those that were specifically asked about the condition.

Causes and Risk Factors

The exact cause of MS is not known. MS is a neurological disease believed to be the result of a complex combination of environmental, genetic, and autoimmune factors.(13) Some people believe MS is an autoimmune disease while others believe it is triggered by exposure to environmental triggers such as viruses, trauma, or heavy metals. Three well-established risk factors for developing MS include being female, being white, and having a high socioeconomic status. Each of these factors increases the risk of developing MS by approximately two-fold.(29)

Risk factors associated with MS are listed below. It is possible to develop MS with or without the risk factors listed below. However, the more risk factors a person has, the greater their likelihood of developing MS. Risk factors for MS include the following:

1. Age. Risk appears to be greatest between the ages of 16 and 40; this is when most people with MS are diagnosed.(5,9,30,31)
2. Gender. At younger ages, women tend to be diagnosed as having MS more frequently than men. However, the gender ratio is more equally balanced in people who develop MS later in life. Since more women than men have MS, it is possible that hormones play a role in developing MS. Being female produces roughly a two-fold increased risk for developing MS.(5,9,13,30-32)
3. Genetic Factors. There may be a genetic component to MS. It is more common in people of Northern European descent, and sometimes it occurs in families. The risk to children of people affected by MS is less than 5 percent over their lifetime. An identical twin of someone with MS has a 25% chance of developing the disease while the dizygotic twin concordance rate is 2% to 5%. The general population prevalence for MS is approximately 0.1%. This is in contrast to the familial MS recurrence risk for primary relatives where parents have a 3% risk, daughters have a 5% risk, and sons have a 1% risk. This is in turn slightly higher than that for extended relatives where uncles/aunts have a 2% risk, nieces/nephews have a 2% risk, and first cousins have a 1% risk. Researchers suspect that more than one gene may be involved and that the tendency to develop multiple sclerosis is inherited, but that the disease may manifest only when environmental triggers are present.(5,9,13,30-32)
4. Ethnic Background. As previously mentioned, MS is more common in people of Northern European descent, especially people who are of Scandinavian background. Being white produces roughly a two-fold increased risk for developing MS.(5,9,30-32)
5. Viral Triggers. Many viruses and bacteria have been suspected of causing MS, most recently the Epstein-Barr virus and the Human Herpes Virus 6 (both in the herpes family), known also for causing infectious mononucleosis. A number of other viruses may be triggers for MS including HTLV-1, measles, mumps, canine distemper, and corona viruses. However, researchers are not positive which virus or viruses are responsible for triggering MS. Some medical experts believe that it is the way certain people respond to the virus that may trigger the disease. Some studies have suggested that developing infection at a critical period of exposure may lead to conditions conducive to the development of MS ten years or more later.(5,9,13,30-32)

6. Vitamin D and Sunlight Deficiencies. According to the U.S. Centers for Disease Control (CDC) MS Fact Sheet, "Vitamin D has a number of effects on the body, mediating cell maturation, calcium homeostasis, and immune system responses. Vitamin D is converted to its hormonally active form 1, 25-dihydroxyvitamin D3 through sunlight exposure in the skin and subsequent hydroxylation in both the liver and the kidney. In MS, Vitamin D is felt to be protective through its immunomodulating effects such as promoting anti-inflammatory cytokines, stimulation of Th2 cells and inhibition of pathologic Th1 cells. Through decreased sun exposure or inadequate intake, Vitamin D deficiency states may increase the risk for MS or alter the course of the disease."(32)
7. Geographical factors. For unknown reasons, multiple sclerosis seems to be more common in geographic areas with temperate climates, including Europe, southern Canada, northern United States, and southeastern Australia. Similarly, MS seems to be more common in people who grow up in a colder climate, as opposed to a tropical climate. A person moving to a tropical locale before age 15 often adopts the lower risk of developing MS associated with warmer climates. The opposite happens if the person moves to a colder climate before age 15. Moving after age 15 does not change the risk. Why and how geographical factors affect risk is not known.(5,9,30,31)
8. Smoking. According to the August 2006 Multiple Sclerosis Quarterly Report, "There is growing evidence that smoking may increase the risk for developing MS and negatively impact the disease course. Smoking has been associated with worsening MS symptoms in isolated case reports. Case control studies have produced variable results, but tend to support an increased risk for MS among smokers. Proposed mechanisms that may be implicated in the association between MS and smoking include immunomodulation, cyanide toxicity, free radical formation, and an increased risk for infection in smokers."(32)

Consequences of MS and Potential Impact on Driving

As previously mentioned, symptoms of MS include tingling, numbness, slurred speech, blurred or double vision, muscle weakness, poor coordination, unusual fatigue, muscle cramps, bowel and bladder problems, and paralysis. According to the Association for Driver Rehabilitation Specialists (ADED),(33) special equipment or accommodations may need to be made in helping a person with MS to drive safely.

Health consequences of MS and potential impacts on driving as indicated by ADED are listed in Table 5.

Table 5. Health Consequences of MS and Potential Impacts on Driving

MS Health Consequences	Potential Impacts on Driving
Loss of physical strength Numbness and tingling Muscle weakness Muscle cramps Paralysis	Decreased functional ability to control vehicle Distractions from driving task, especially in the case of painful muscle cramps Reduced reaction time
Loss of range of motion in arms	Decreased functional ability to control vehicle Reduced reaction time
Spasticity Poor coordination	Decreased functional ability to control vehicle Reduced reaction time
Involvement of visual system	May not meet vision standard (this may be transient or permanent) May lose binocular vision (transient or permanent) Night driving may be impacted (transient or permanent) Susceptible to problems with glare (transient or permanent) May develop double vision (transient or permanent) May lose peripheral vision (transient or permanent) May lose color vision (transient or permanent) Lengthening of reaction time while "trying to see"
Decreased problem solving Decreased memory	May be limited to familiar routes Increased reaction time Decreased ability to problem solve in emergencies - as in cases when an accident could be avoided with quick thinking
Unregulated emotions Overly emotional Upset, angry, frustrated, depressed	Difficulty focusing on driving task
Decreased energy	Decreased ability to drive long distances Problems with loading
Loss of mobility	Deceased ability to get in and out of the vehicle
Medications (See section VII)	Primary concern is development of drowsiness

Parkinson's Disease (PD)

PD, a movement disorder,(34-36) is chronic and progressive. Brain cells located in the substantia nigra of the brain malfunction and die. These cells produce dopamine, and the amount of dopamine in the brain decreases accordingly. When the normal amount of dopamine is reduced, nerve cells do not easily transmit nerve impulses from cell to cell, and messages indicating that it is time for the body to move are not sent correctly. A person can no longer control his or her movement normally.(34-36) Symptoms of PD include tremors of the hands, arms, legs or jaw; a distinctive gait; muscle stiffness of the limbs and trunk; unusual slowness of movement (bradykinesia); stooped posture and postural instability; falling or jerking uncontrollably; impaired balance and coordination; rigidity; and dementia.

Diagnosis and Screening

There is no standard test to diagnose PD. It can be difficult to diagnose, but it can be diagnosed by a skilled neurologist. A neurologist may order tests to rule out other disorders and may rely on a neurological examination and the description of symptoms by the patient.(33,34)

Diagnosis depends on the presence of at least two of the three major signs of PD: tremor at rest, rigidity, and bradykinesia, as well as the absence of a secondary cause, such as antipsychotic medications or multiple small strokes in the regions of the brain controlling movement. Tremors and bradykinesia seem to be more easily detected by patients than rigidity.(33-36)

The neurological examination might involve the following tests of reactions, reflexes, and movements: '(a) determining how quickly the person can tap the finger and thumb together, or tap the foot up and down to assess Bradykinesia; (b) determining tremor by visual inspection; (c) assessing rigidity by moving the neck, upper limbs, and lower limbs while the patient relaxes, feeling for resistance to movement; and (d) testing postural instability with the "pull test," in which the examiner stands behind the patient and asks the patient to maintain their balance when pulled backwards. The examiner pulls back briskly to assess the patient's ability to recover, being careful to prevent the patient from falling.'(37)

Patients should be checked for exposure to medications that can block dopamine function in the brain. Many drugs with similar properties are also used for other purposes, and the neurologist will ask the patient about these drugs. Table 1 below contains a list of these medications.(37)

Table 6. Drugs That Can Block Dopamine Function(37)

Generic	(Trade Name)
Acetophenazine	(Tindal®)
Amoxapine	(Asendin®)
Chlorpromazine	(Thorazine®)
Fluphenazine	(Permitil®, Prolixin®)
Haloperidol	(Haldol®)
Loxapine	(Loxitane®, Daxolin®)
Mesoridazine	(Serentil®)
Metoclopramide	(Reglan®)
Molindone	(Lindone®, Moban®)
Perphenazine	(Trilafon® or Triavil®)
Piperacetazine	(Quide®)
Prochlorperazine	(Compazine®, Combid®)
Promazine	(Sparine®)
Promethazine	(Phenergan®)
Thiethylperazine	(Torecan®)
Thioridazine	(Mellaril®)
Thiothixene	(Navane®)
Trifluoperazine	(Stelazine®)
Triflupromazine	(Vesprin®)
Trimeprazine	(Temaril®)

Course of Disease

Parkinson's usually begins in patients around age 60, but it can begin earlier. The early warning signs of PD include tremors, muscle stiffness, unusual slowness, and a stooped posture. Medications can control initial symptoms, but as time goes on they become less effective. As the disease worsens, patients develop tremors, causing them to fall or jerk uncontrollably (dyskinesias). At other times, rigidity sets in and makes patients unable to move. About one-third of the patients develop dementia, an impairment of cognition and thought processes.(36,38)

Parkinson's is not considered to be a fatal disease. However, it is progressive and symptoms do worsen over time. Eventually, patients have a very compromised quality of life and are often unable to perform daily movement functions, included getting out of bed unaided or driving. They may also have problems such as depression, sleep problems, or trouble chewing, swallowing, or speaking. Most people are forced to stop working due to the progressively disabling symptoms. Life-threatening complications such as pneumonia, can also develop.(35,36,38)

Forms. There seem to be six different forms that PD and/or Parkinsonism symptoms can take. These are presented and described in Table 7 below.

Table 7. Types of Parkinsonian Syndromes

Type of Parkinson's Disease or Pseudoparkinsonism	Description
Postencephalitic Parkinsonism	"A disabling neurological disorder which often develops years after the acute phase of the viral disease, encephalitis lethargica, had passed. Also called "sleeping sickness." Other viral infections that can induce Parkinson symptoms include: western equine encephalomyelitis, eastern equine encephalomyelitis and Japanese B encephalitis."(36)
Drug Induced Parkinsonism	"Drugs that can produce Parkinsonian symptoms include: chlorpromazine and haloperidol, drugs which are prescribed for psychiatric patients, metoclopramide, often used to treat stomach disorders, and reserpine, a blood pressure controlling drug. Changing the medication or adjusting the dosage can moderate or eliminate the symptoms."(36)
Striatonigral Degeneration	"This condition is characterized by mild problems in the substantia nigra, but severe damage to other parts of the brain that usually are less affected by primary Parkinson's disease. Patients with striatonigral degeneration usually have greater muscular rigidity, and their disease progresses rapidly."(36)
Arteriosclerotic Parkinsonism or Pseudoparkinsonism	"A condition in which multiple small strokes cause damage to blood vessels in the brain, arteriosclerotic Parkinsonism rarely causes tremors, but most people afflicted with it suffer dementia. The usual drugs used to treat Parkinsonian symptoms are largely ineffective with pseudoparkinsonism."(36)
Toxin-Induced Parkinsonism	"Some toxins are known to cause Parkinsonism. These include manganese dust, carbon disulfide, carbon monoxide and a chemical known as MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine)."(36)
Parkinson's symptoms as part of other neurological disorders	"Parkinson's symptoms may emerge in conjunction with: progressive supranuclear palsy, Huntington's disease, Alzheimer's disease, Creutzfeldt-Jakob disease, and post-traumatic encephalopathy."(36)

Levels of Severity

As previously indicated, there are currently no blood or laboratory tests that have been proven to help in diagnosing PD. The diagnosis is based on medical history and a neurological examination. The disease can be difficult to diagnose accurately.

The Unified Parkinson's Disease Rating Scale (UPDRS) is the primary clinical tool used to assist in diagnosis and determine severity of PD. It is made up of four sections: (1) mentation, behavior, and mood; (2) activities of daily living; (3) motor; (4) complications of therapy using categories that range

from no symptoms to very severe symptoms depending upon the area being assessed. The scale is evaluated by interview and clinical observation. Some sections require multiple grades assigned to each extremity. Clinicians and researchers use the UPDRS and the motor section in particular to follow the progression of a person's PD.(39-41)

Additional rating scales that are commonly used to assess levels of severity in individuals with PD include the Hoehn and Yahr Stage and the Schwab and England Activities of Daily Living Scale. On the Hoehn and Yahr Stage, patients are rated on a scale ranging from "no sign of disease" to "wheelchair bound or bedridden unless aided." With regard to the Schwab and England Activities of Daily Living Scale, patients are rated on a scale ranging from completely independent to vegetative states.

A copy of the UPDRS , the Schwab and England Activities of Daily Living Scale, and the Hoehn and Yahr Stage scale is presented in Appendix I.(39-41) Pdf versions of the rating scales and data form can be downloaded from Movement Disorder Virtual University at http://www.mdvu.org/library/ratingscales/pd/upddf.pdf. The Movement Disorders Virtual University has created a list of PD categories and associated assessments as follows:(40)

1. Dystonia Rating Scales and Scoring Sheets
   - Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)
   - Global Dystonia Scale/GDS
   - Unified Dystonia Rating Scale/UDRS
   - Fahn-Marsden Scale and Scores
2. Essential Tremor
   - Tremor Assessment Form
3. Myoclonus
   - The Unified Myoclonus Rating Scale
4. PD
   - Unified Parkinson's Disease Rating Scale
   - Unified Parkinson's Disease Data Form
5. Progressive Supranuclear Palsy
   - Progressive Supranuclear Palsy Rating Scale and Staging System
6. Restless Legs Syndrome
   - Restless Legs Syndrome Rating Scale and Scoring Sheet
7. Spasticity
   - Spasticity Rating Scales and Office Data Form

Prevalence and Incidence

Prevalence and incidence estimates for PD are not easily found. CDC PD data collection banks and countrywide public health repositories of PD cases do not seem to exist, although some city and county

repositories do. Furthermore, the methods used to estimate the number of people with PD vary around the world and in the United States. Consequently, prevalence and incidence figures are reported from various studies and organizations in Table 8.

Table 8. Prevalence and Incidence Estimates of PD

Source	Year	City and/or Country	Prevalence	Incidence
American Parkinson Disease Association(42)	2000	USA	1,000,000 people	
Michael J. Fox Foundation(43)	2008	USA	1,500,000 people	
Viartis(44)	2007	USA	107 to 329 per 100,000 1 per 625 people Mean onset of 55 years of age.	40,000 new cases per year; 13-20.5 per 100,000 per yr
		Canada	125 per 100,000	
		Ethiopia	7 per 100,000	
PD registry in Nebraska(45)	2004	Nebraska, USA	329.3 per 100,000	
Door to door survey(46)	1985	Copiah County, MS	347 per 100,000 for people age 40 and older. No significant differences in age-adjusted prevalence ratios by race or gender were found. Prevalence increased with increasing age.	
Kaiser Permanente Medical Care Program(47)	1994-1995	Northern California		13.4 per 100,000 Incidence rapidly increased over the age of 60 years, with only 4% of the cases being under the age of 50 years. The rate for men (19.0 per 100,000) was 91% higher than that for women (9.9 per 100,000). The age- and gender-adjusted rate per 100,000 was highest among Hispanics (16.6), followed by non-Hispanic Whites (13.6), Asians (11.3), and Blacks (10.2). These data suggest that the incidence of Parkinson's disease varies by race/ethnicity.
University of Tartu, Estonia(48)	2002	World	18 to 207 per 100,000, age adjusted Caucasian - 56 to 190 per 100,000 Asian - 61 to 140 per 100,000 African Blacks - 4 to 31 per 100,000	
		Estonia	152 per 100,000	16.8 per 100,000 per yr
NeurologyChannel, Health Communities.com(38)	2008	World	1 to 1.5 million people have PD worldwide Occurs in all races but is more prevalent in Caucasians. Men are affected more than women. Average age of onset is 60 yrs, and 5-10% have symptoms before they are 40 years old. Risk increases with age.	
General Practice Survey in Australia(49)	2006	Queensland, Australia	146 per 100,000	

Source	Year	City and/or Country	Prevalence	Incidence
Parkinson Society Canada(50)	2008	Canada	100-200 per 100,000	10 to 20 per 100,000 per year 85% of those diagnosed are over 65 years old.
Community Based Survey in Singapore(51)	2004	Singapore	For 50+ year olds: Singapore - .30% and increased significantly with age. Singapore Chinese - .33% Singapore Malaysians - .29% Singapore Indians - .28%	
The Rotterdam Study(52)	2004	Netherlands		The study was conducted on people aged 55 and older. The incidence of parkinsonism and PD increased with age, with incidence rates for PD increasing from 0.3 per 1000 person-years in subjects aged 55 to 65 years, to 4.4 per 1000 person-years for those aged ≥85 years. The overall age-adjusted incidence rate of any parkinsonism was not different in men and women, but men seem to have a higher risk for PD (male-to-female ratio, 1.54).
Manhattan Disease Registry and Medicare Patients(48)	1988-1991	Northern Manhattan, NY	107,000 per 100,000 Age-adjusted prevalence rates were lower for women than for men in each ethnic group and were lower for blacks than for whites and Hispanics..	13 per 100,000 Incidence rates were highest among black men, but they were otherwise comparable across the sex and ethnic groups. The estimated cumulative incidence up to age 90 years was lower for women than for men. By ethnic group, the cumulative incidence was higher for blacks than for whites and Hispanics, but more deaths occurred among incident black cases

In summary, the prevalence of PD in the United States is likely somewhere in the range of 107 to 329 per 100,000 individuals. The incidence of PD in the United States seems to be about 13 to 20.5 people per 100,000 or 40,000 new cases per year. Both men and women are afflicted, and the probability of developing PD increases with advancing age. The PD rate for men seems to be higher than for women, and the average age of onset seems to be around 55 to 62 years old. The onset of PD before age 30 is rare. However, about 10% of PD patients have symptoms by age forty and 15% are diagnosed before the age of 50.(34) Prevalence rates for PD seem to be highest for Caucasians, followed in order by Asians and African Americans. However, there is evidence in California that Hispanics may be affected as much as or more than Caucasians, and there is evidence in New York that incidence rates are highest for black males. There seem to be no data to report on prevalence of PD in CMV drivers.

Causal and Risk Factors.

The cause of PD is unknown. Many researchers believe that several factors are involved: free radicals, accelerated aging, environmental toxins, and genetic predisposition. A list of risk factors for PD follows:

1. Gender. Males are about 1.5 times more likely to get Parkinson's than females. Some researchers theorize that estrogen may have neuroprotective effects. Consistent with this idea

is the finding that postmenopausal women who do not use hormone replacement therapy seem to be at greater risk, as are those who have had hysterectomies. Furthermore, a gene predisposing someone to Parkinson's may be linked to the X chromosome.(34,35,38,53-55)

2. Age. The risk of PD increases with age, as PD generally manifests in the middle or late years of life (age of onset ranges from 35 to 85). Dysfunctional antioxidative mechanisms are associated with older age. Perhaps the acceleration of age-related changes in dopamine production may be a factor. Some researchers assume that people with Parkinson's have neural damage from genetic or environmental factors that get worse as they age.(34,35,38,53-55)
3. Environmental Toxins. Exposure to environmental toxins and chemicals, such as herbicides and pesticides which inhibit dopamine production and produce free radicals and oxidation damage, may be involved. Those involved in farming and are exposed to pesticide toxins have a greater prevalence of Parkinson's symptoms. People who live in a rural area, drink well water, or live on a farm (perhaps due to an increased exposure to herbicides and pesticides) have a higher rate of PD.(34,35,38,53-55) The world's highest prevalence of PD is in the vicinities of ferromanganese plants near Brescia in Italy, where the PD prevalence rate is about 407 per 100,000 people. Manganese concentrations in dust have been found to be significantly higher around and downwind from the ferromanganese plants. In high concentrations, manganese is a known cause of PD.(34,35,38,44,53)
4. Genetics. In a small number of cases worldwide there is a strong inheritance pattern. Roughly one-fifth of PD patients have at least one relative with Parkinsonian symptoms. A genetic predisposition for PD is possible, with the onset of disease and its gradual development dependant on a trigger, such as trauma, other illness, or exposure to an environmental toxin.(34,35,38,54,55) Several genes that cause symptoms in younger patients have been identified. A Mayo Clinic led international study suggested that the gene alpha-synuclein may play a role in developing the disease. Studies showed that individuals with a more active gene had a 1.5 times greater risk of developing Parkinson's. People with abnormal genes seem to develop PD at an earlier age, before the age of 50, and this type of Parkinson's tends to run in families. Regardless, most PD occurs in people over the age of 60, and the role of genetics in these people is unknown. Researchers at Albert Einstein College of Medicine and Beth Israel Medical Center in New York discovered a single genetic mutation on a gene called LRRK2 (leucine-rich repeat kinase 2) that accounts for as many as 30% of the cases of PD in Arabs, North Africans, and Jews. It seems that people with the mutation make an abnormal version of a protein called dardarin in which a single amino acid is glycine instead of serine. However, most researchers believe that most cases are not caused by genetic factors alone.(38,53,54,56,57)
5. Free Radicals. It may be that free radicals are involved in the degeneration of dopamine-producing cells. Free radicals add an electron by reacting with nearby molecules in a process called oxidation, which can damage nerve cells. If antioxidative chemicals and processes fail to protect dopamine-producing nerve cells, they could be damaged and, subsequently, PD could develop.(35,36,38)

6. Low Levels of Vitamin B Folate. Some researchers have discovered that mice with a deficiency of this vitamin developed severe Parkinson's symptoms, while those with normal levels did not.(53)
7. Head Trauma. According to Parkinson's.org, "Recent research points to a link between damage to the head, neck, or upper cervical spine and Parkinson's. A 2007 study of 60 patients showed that all of them showed evidence of trauma induced upper cervical damage. Some patients remembered a specific incident, others did not. In some cases Parkinson's symptoms took decades to appear."(53)
8. Low Estrogen Levels. Reduced estrogen levels may increase the risk of PD. This means that menopausal women who receive little or no hormone therapy (HT) and those who have had hysterectomies may be at higher risk. Menopausal women using HT appear to have a decreased risk.(55)

Potential Impact on Driving Performance

The primary health consequences of PD and their potential impacts on driving ability are listed in Table 9.(38,58,59)

Table 9. PD Primary Health Consequences and Potential Impacts on Driving(36,38,58-61)

PD Health Consequences	Potential Impacts on Driving
Bradykinesia - produces difficulty initiating movement as well as difficulty completing movement once it is in progress.	Inability or decreased ability to turn steering wheel, use the gas pedal, and push down the brake. Slow reaction time/Inability to react quickly to road hazards. Decreased ability to drive, especially in emergency conditions.
Tremors – specifically in the hands, fingers, forearm, or foot - tend to occur when limb is at rest and not when performing tasks.	Decreased focus on driving. Increased potential to hit the wrong pedal or "button." Inability to drive long distances without tremors.
Rigidity – muscles "stiffen" may produce muscle pain. Rigidity tends to increase during movement. Muscle weakness.	Decreased ability to perform quick actions. Increased reaction time. Decreased ability to use steering wheel or gas or brake pedals. Decreased ability to control steering or speed.
Difficulty with visuo-spatial organization, visual planning and judgment, and contrast sensitivity.(59,61)	May not be able to see well enough to drive. Difficulty reading signs and signals. Decreased depth perception.

The progressive loss of voluntary and involuntary muscle control produces a number of secondary symptoms associated with PD. Most patients do not experience all the secondary symptoms which vary in intensity from person to person. Secondary health consequences and their potential impacts on driving are listed in Table 10.(38,58,59)

Most people with PD do not develop all the symptoms associated with the disease. The disease may progress quickly or gradually over years. Many people become profoundly disabled and others function relatively well. Symptoms may vary from day to day or even moment to moment. There is no known reason for the fluctuation of symptoms, although they may be due to the disease process or to medication. Symptoms are hard to predict, but they have potential for affecting driving.(38,58)

Table 10. Secondary Health Consequences of PD and Potential Impacts on Driving(38,58-61)

Secondary Health Consequence	Potential Impact on Driving
Constipation	Decreased ability to drive long distances Distraction due to pain
Difficulty swallowing (dysphagia)–saliva and food that collects in the mouth or back of the throat may cause choking, coughing, or drooling	Possible distraction Choking hazard
Excessive sweating (hyperhidrosis)	Limited impact - unless hands get very wet
Loss of bladder and/or bowel control (incontinence)	Decreased ability to drive long distances Distraction while driving
Reductions in cognitive function	Decreased ability to problem solve and make reasoned decisions Impaired reasoning Slow reaction time Decreased ability to switch attention between competing tasks(61) Problems with attention Difficulties with planning and judgment(59)

Driving is a complicated task. Driving safely depends on a person's emotional, physical, and cognitive well-being.(60) People in the early stages of the disease are most likely able to drive, especially if they take medications that control their symptoms. There are ADED specialists who can assess how and if PD is affecting a patient's driving. Patients may receive training so they can drive better, if they are still able to drive safely with PD.(58,61)

Parkinson's Disease, Multiple Sclerosis, and Driving Regulations

Current United States Federal Regulatory and Medical Advisory Criteria for CMV Operators

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

Medical advisory criteria for evaluation of CMV drivers appear in 49 CFR 391.41.(http://www.fmcsa.dot.gov/rules-regulations/administration/medical.htm). The subsections relevant to PD and MS are presented below.

391.41(b)(7)

A person is physically qualified to drive a CMV if that person:

Has no established medical history or clinical diagnosis of a rheumatic, arthritic, orthopedic, muscular, neuromuscular or vascular disease which interferes with the ability to control and operate a commercial motor vehicle.

Certain diseases are known to have acute episodes of transient muscle weakness, poor muscular coordination (ataxia), abnormal sensations (paresthesia), decreased muscle tone (hypotonia), visual disturbances and pain which may be suddenly incapacitating. With each recurring episode, these symptoms may become more pronounced and remain for longer periods of time. Other diseases have more insidious onsets and display symptoms of muscle wasting (atrophy), swelling and paresthesia which may not suddenly incapacitate a person but may restrict his/her movements and eventually interfere with the ability to safely operate a motor vehicle. In many instances these diseases are degenerative in nature or may result in deterioration of the involved area.

Once the individual has been diagnosed as having a rheumatic, arthritic, orthopedic, muscular, neuromuscular or vascular disease, then he/she has an established history of that disease. The physician, when examining an individual, should consider the following:

(1) The nature and severity of the individual's condition (such as sensory loss or loss of strength);

(2) The degree of limitation present (such as range of motion);

(3) The likelihood of progressive limitation (not always present initially but manifest itself over time);

(4) The likelihood of sudden incapacitation.

If severe functional impairment exists, the driver does not qualify. In cases where more frequent monitoring is required, a certificate for a shorter period of time may be issued.

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

391.41(b)(9)

A person is physically qualified to drive a CMV if that person:

Has no mental, nervous, organic, or functional disease or psychiatric disorder likely to interfere with the driver's ability to drive a CMV safely.

Emotional or adjustment problems contribute directly to an individual's level of memory, reasoning, attention, and judgment. These problems often underlie physical disorders. A variety of functional disorders can cause drowsiness, dizziness, confusion, weakness, or paralysis that may lead to incoordination, inattention, loss of functional control, and susceptibility to crashes while driving. Physical fatigue, headache, impaired coordination, recurring physical ailments, and chronic "nagging" pain may be present to such a degree that certification for commercial driving is inadvisable. Somatic and psychosomatic complaints should be thoroughly examined when determining an individual's overall fitness to drive. Disorders of a periodically incapacitating nature, even in the early stages of development, may warrant disqualification.

391.41(b)(9) is potentially relevant because certain individuals with PD and MS may have cognitive impairment that could impact their driving ability. Those paragraphs from 391.41(b)(9) that pertain specifically to psychiatric disorders are not relevant to this evidence report and have been removed from this section.

Current Medical Qualification Guidelines

In 1988, the FMCSA published the outcome of a conference to review the current medical standards covering neurological disorders (see: http://www.fmcsa.dot.gov/facts-research/research-technology/publications/medreports.htm), which included suggestive information for patients with neurological disorders. Unlike standards which are regulations that a medical examiner must follow, these proposals are recommendations that the medical examiner is advised to follow. While not law, the correspondence is suggestive for medical examiners as a standard of practice. The task force felt that the current medical examination for commercial driving certification was inadequate for assessing neurological conditions. The task force recommends that any applicant having neurological signs or symptoms be referred to a neurologist for more detailed and qualified evaluation of neurological status in relation to certification for driving commercial vehicles. This specialist would be provided guidelines for evaluating certification of applicants. For progressive neurological disorders, we recommend two

categories for disqualification. The first category includes chronic diseases that would unequivocally indicate disqualification[1]:

- Dementia
- Motor neuron disease
- Malignant tumors of the central nervous system
- Huntington's disease
- Wilson's disease

The second category includes diseases for which disqualification would be likely; however, appeal of this decision under specified conditions would be possible:

- MS
- Peripheral neuropathies
- Myopathies
- Neuromuscular junction disorders
- Benign brain tumors
- Dyskinesias
- Treatable dementias
- Cerebellar ataxies

Task Force II Report: Progressive Neurological Conditions

In the opinion of the task force, any individual with one of the progressive neurological disorders as defined above should be disqualified from driving a commercial vehicle, unless specifically granted a waiver by a medical or surgical neurologist or physiatrist upon determination that any neurological impairment will not interfere with his/her ability to control and safely operate such a vehicle.

MULTIPLE SCLEROSIS

According to the task force, patients with acute, chronic, or relapsing progressive MS often accumulate incremental neurological dysfunction involving multiple functional subsystems of the central nervous system at multiple levels. The multiplicity of neurological dysfunction causes complex disorders of integrated sensory-motor and, in some cases, cognitive function which exceeds the simple sum of individual neurological deficits. In addition, there is a potential for unpredictable relapses at any time and patients with progressive MS characteristically suffer from excessive fatigability and daily fluctuations in motor performance. Prolonged physical activity, emotional stress, warm ambient climate, and minor viral infections are common conditions which are known to transiently worsen neurological function in these patients.

Disposition

[1] Appeal would be possible only for changes in and/or verification of diagnosis. Appeal would include evaluation by a board-certified or eligible neurologist, neurosurgeon, or physiatrist. Specific evaluation criteria developed by the task force include successful completion of neurologic history and examination, driving skills testing, or equivalent functional testing. If an individual is certified after this process, he/she would be required to have an on-the-road driving test. For individuals who have successfully appealed, an annual evaluation would be required.

The complex disorder of integrated sensory-motor function seen in acute, chronic, or relapsing progressive MS is not compatible with the level of motor skill required for operation of commercial vehicles, and these patients should not be approved for licensure.

Some patients with clinically definite MS may have a benign course with minimal neurological dysfunction being present even 10 to 15 years after the onset of the disease. The task force recommends that patients with clinically benign MS for a duration of at least five years after diagnosis, and patients with possible or probable MS, may be considered candidates for licensure to operate a commercial vehicle if the following conditions apply:

- There are no signs of relapse or progression.
- There are no or only functionally insignificant neurological signs and symptoms as determined by a neurologist.
- An MRI and triple-evoked potential studies are normal or do not reveal new lesions compared to prior evaluations made at least one year apart.
- There is no history of excessive fatigability or periodic fluctuations of motor performance especially in relation to heat, physical and emotional stress, and infections.

The disqualification may be appealed to a neurologist or physiatrist who may recommend a simulated driving skills test or equivalent functional test (see Appendix A). If an applicant wins an appeal, then an on-the-road driving test is required before final certification. In order to detect subsequent signs of progression, the candidate will be reevaluated annually by a neurologist*, who may again recommend functional testing (see Appendix A of Task Force Document), and will require a repeat on-the-road driving test.

PARKINSONISM

According to the task force, parkinsonism is a chronic progressive syndrome of insidious onset manifesting a triad of muscular rigidity, slowness of movement (bradykinesia), and tremor plus associated postural abnormalities including a stooped posture, interosseal hand, and clawing of the toes. The most common form of parkinsonism is PD. Its prevalence is approximately 1% of the population over age 60. It is the second most common degenerative disease, following Alzheimer's disease. A variety of disorders recognized as separate morbid entities such as progressive supranuclear palsy, olivopontocerebellar atrophy, Wilson's disease, and several different types of dominantly inherited cerebellar ataxias may present as parkinsonism.

The major disabilities inflicted by PD with reference to the operation of commercial vehicles is the bradykinesia. This is a complex disorder of motor function involving prolonged motor and premotor reaction times, slowness of execution of movement, frequent interruptions of ongoing movement, and a marked paucity of spontaneous automatic movements. Characteristically, patients are largely unaware of mild to moderate degrees of bradykinesia, which may significantly impair capability to operate a commercial vehicle.

These difficulties may predate the development of symptoms sufficient to bring a patient to medical attention. Therefore, it is not a rare occurrence for accidents to be the initial manifestation of the disease. Corresponding impairment in mental function, bradyphrenia, slowness in changing motor sets, and difficulty in the perception of visual space may also contribute to difficulties in the operation of a commercial vehicle. Significant dementia with impairment of recent memory occurs in as many as 20% to 40% of patients with Parkinson's disease though usually not until later in its course when the diagnosis is already established. A particularly problematic characteristic of parkinsonism is the difficulty of carrying on two or more tasks simultaneously. This is a defect that would particularly impair the ability to operate a commercial vehicle. Additionally, depression, fatigability, and panic attacks are frequent accompaniments of PD.

The following signs and symptoms may be associated with PD:

- Weakness
- Lethargy
- Depression
- Headache
- Muscle cramps
- Unsteadiness in walking
- Shuffling
- "Freezing"
- Festinating gait
- Low back pain
- Impotence
- Bowel and bladder disturbances

Disposition

The task force recommends that patients with parkinsonism of any etiologic type should be disqualified from driving commercial vehicles. Patients with iatrogenic parkinsonism induced by medication may recover from their Parkinson syndromes and regain qualification. However, the conditions for which the responsible medications were prescribed may themselves be causes for exclusion.

Appeal

Patients with PD who are receiving effective symptomatic treatment may appeal the ruling to a board-certified or eligible neurologist, neurosurgeon, or physiatrist who may recommend a simulated driving skills test or equivalent functional test (see Appendix A). If an applicant wins an appeal, then an on-the-road driving test is required before final certification. These individuals may be licensed to drive commercial vehicles provided:

- The medication is well tolerated and there are no side effects.
- There is no significant fluctuation or "on-off" effect.
- There is good compliance.
- There are no mental deficits.

In order to detect subsequent signs of progression, the candidate will be reevaluated annually by a board-certified or eligible neurologist, neurosurgeon, or physiatrist who may again recommend functional testing and will require a repeat on-the-road driving test.

Additional information on Neurological Disorders and Commercial Drivers is supported at http://www.fmcsa.dot.gov/rulesregs/medreports.htm.

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

Current medical fitness standards and guidelines for individuals performing commercial transportation in the United States are summarized in Table 11. Included in the table are pertinent rules and guidance for pilots, railroad workers, and merchant mariners. None of the agencies have standards or guidelines specific for PD or MS. FAA is the most focused, with specific neurologic standards that include reference to PD and MS among a multitude of neurological disorders. PD is listed under extrapyramidal, hereditary, and degenerative diseases of the nervous system for which a complete neurological evaluation is necessary to determine eligibility for medical certification. MS is listed under demyelinating diseases for which a neurological and/or general medical consultation is necessary (in most instances) for determination of eligibility for medical certification. The Merchant Mariner Guidelines are less specific, but they have a small section on neurological disorders that are potentially disqualifying conditions. PD is listed as one of the conditions that may seriously limit balance or coordination, hence it is potentially disqualifying. MS is not specifically mentioned in this document. The document also includes a general description of the functional abilities required for the job of merchant mariner. The FRA has no specific medical standards for neurologic disorders.

Table 11. Standards and Guidelines for Neurologic Disorders from U.S. Government Transportation Safety Agencies

Condition	FAA (all classes of airmen)	Railroad†	Merchant Mariner‡
Neurologic	Electronic Code of Federal Regulations (e-CFR) **Title 14: Aeronautics and Space** PART 67—MEDICAL STANDARDS AND CERTIFICATION Subpart B—First-Class Airman Medical Certificate § 67.109 Neurologic. Neurologic standards for a first-class airman medical certificate are: (a) No established medical history or clinical diagnosis of any of the following: (1) Epilepsy; (2) A disturbance of consciousness without satisfactory medical explanation of the cause; or (3) 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— (1) Makes the person unable to safely perform the duties or exercise the privileges of the airman certificate applied for or held; or (2) 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. http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=b0859a44f58f555dbdc7660c19c131c6&rgn=div8&view=text&node=14:2.0.1.1.5.2.1.5&idno=14	With few exceptions, most railroads have no specific medical standards	PHYSICAL EVALUATION GUIDELINES FOR MERCHANT MARINER'S DOCUMENTS AND LICENSES BACKGROUND. a. Various regulations in Title 46, Code of Federal Regulations (CFR), Parts 10, 12, and 13 require individuals to be physically qualified to hold certain merchant mariner's licenses and documents. With the exception of visual acuity and color vision, these regulatory requirements are not specified. The physician conducting the physical examination makes the initial determination whether or not the seaman is "fit for duty," that is, physically qualified to carry out his or her duties and responsibilities. However, there are medical conditions that cannot be routinely detected during a physical examination, unless the mariner discloses the symptoms or conditions, such as sleep disorders. It is recommended that medical personnel conducting physicals question mariners about these areas. b. Regulation I/9 of the International Convention on Standards of Training, Certification, and Watchkeeping for Seafarers (STCW) requires each party to establish standards of medical fitness for seafarers. The medical standards listed in this NVIC are also the United States' standards for meeting the STCW's regulation. c. Without specific guidelines for conducting the examination, or without a general familiarity with and appreciation for the rigors of employment in the maritime environment, most medical personnel are unable to fully evaluate the applicant's medical qualifications; therefore, this NVIC provides guidance to assist medical personnel in conducting these examinations.

Condition	FAA (all classes of airmen)	Railroad†	Merchant Mariner‡
	Guide for Aviation Medical Examiners **Decision Considerations** **Aerospace Medical Dispositions** **Item 46. Neurologic** A history or the presence of any neurological condition or disease that potentially may incapacitate an individual should be regarded as initially disqualifying. Issuance of a medical certificate to an applicant in such cases should be denied or defer, pending further evaluation. A convalescence period following illness or injury may be advisable to permit adequate stabilization of an individual's condition and to reduce the risk of an adverse event. Applications from individuals with potentially disqualifying conditions should be forwarded to the AMCD. Processing such applications can be expedited by including hospital records, consultation reports, and appropriate laboratory and imaging studies, if available. Symptoms or disturbances that are secondary to the underlying condition and that may be acutely incapacitating include pain, weakness, vertigo or incoordination, seizures or a disturbance of consciousness, visual disturbance, or mental confusion. Chronic conditions may be incompatible with safety in aircraft operation because of long-term unpredictability, severe neurologic deficit, or psychological impairment. The following lists the most common conditions of aeromedical significance, and course of action that should be taken by the examiner as defined by the protocol and disposition in the table. Medical certificates must not be issued to an applicant with medical conditions that require deferral, or for any condition not listed that may result in sudden or subtle incapacitation without consulting the AMCD or the RFS. Medical documentation must be submitted for any condition in order to support an issuance of an airman medical certificate. Cerebrovascular Disease (including the brain stem) Demyelinating Disease Extrapyramidal, Hereditary, and Degenerative Diseases of the Nervous System Headaches Hydrocephalus and Shunts Infections of the Nervous System		4. DISCUSSION. a. For a vessel to be operated safely, it is essential that the crewmembers be physically fit and free of debilitating illness and injury. The seafaring life is arduous, often hazardous, and the availability of medical assistance or treatment is generally minimal. As the international trend toward smaller crews continues, the ability of each crewmember to perform his or her routine duties and respond to emergencies becomes even more critical. b. All mariners should be capable of living and working in cramped spaces, frequently in adverse weather causing violent motion of the vessel. Extended workdays are common. All mariners must be able to participate in emergency evolutions such as firefighting or launching lifeboats or liferafts. Members of the deck and engine department must be capable of physical labor, climbing, and handling moderate weights (from 30-60 pounds). c. An applicant for an entry level rating i.e., ordinary seaman, wiper, or steward's department (food handler), does not require a physical examination, but he or she should have the agility, strength, and flexibility to: 1. Climb steep or vertical ladders 2. Maintain balance on a moving deck 3. Pull heavy fire hoses up to 400 feet, and have the ability to lift fully charged fire hoses 4. Rapidly don an exposure suit 5. Step over door sills of 24 inches in height, and 6. Open or close watertight doors that may weigh up to 56 pounds

Condition	FAA (all classes of airmen)	Railroad†	Merchant Mariner‡
	Neurologic Conditions Other Conditions Presence of any neurological condition or disease that potentially may incapacitate an individual Spasticity, Weakness, or Paralysis of the Extremities Vertigo or Disequilibrium http://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/app_process/exam_tech/item46/amd/		An applicant with physical limitations who may not be able to perform the above actions may be issued a Merchant Marine Document (MMD) with suitable limitations. Regional Examination Centers (REC) processing an applicant who is restricted in his or her abilities shall contact the National Maritime Center (NMC-4C) for the appropriate endorsement. d. Enclosure (1) contains standards to guide physicians, physician assistants, and licensed nurse practitioners, in examining merchant seamen. It will also assist Coast Guard licensing personnel in evaluating an applicant's eligibility based on the findings. e. These guidelines are just that—guidelines. They are not intended to be absolute or all encompassing. Some individuals may have other medical conditions or physical limitations which would render them incompetent to perform their duties aboard a vessel. Others may be quite capable of working at sea without posing a risk to themselves, their ship, or shipmates even though one of the listed conditions exists. Any cause for rejection is disqualifying only while the condition persists or is likely to cause disqualifying complications. While each applicant must be evaluated for their physical competence individually, the conditions described in enclosure (1) are those which have been considered disqualifying by the medical and maritime communities. Waivers may be considered where extenuating circumstances are such to warrant special consideration and it can be demonstrated that the applicant can perform safely the duties of the license or merchant mariner document. Requests for waivers will be submitted to the National Maritime Center (NMC-4C) by the REC for review and a final determination.

<table>
<tr><th>Condition</th><th>FAA
(all classes of airmen)</th><th>Railroad†</th><th>Merchant Mariner‡</th></tr>
<tr>
<td></td>
<td>
Aerospace Medical Dispositions
Item 46. Neurologic - Demyelinating Disease[17]
<table>
<tr><th>Disease/ Condition</th><th>Class</th><th>Evaluation Data</th><th>Disposition</th></tr>
<tr><td>Acute Optic Neuritis;

Allergic Encephalo-myelitis;

Landry Guillaume Barre Syndrome;

Myasthenia Gravis; or

Multiple Sclerosis</td><td>All</td><td>Submit all pertinent medical records, current neurologic report, to comment on involvement and persisting deficit, period of stability without symptoms, name and dosage of medication(s) and side effects</td><td>Requires FAA Decision</td></tr>
</table>
[17] Factors used in determining eligibility will include the medical history, neurological involvement and persisting deficit, period of stability without symptoms, type and dosage of medications used, and general health. A neurological and/or general medical consultation will be necessary in most instances.

http://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/app_process/exam_tech/item46/amd/dd/
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5. ACTION.

a. The guidelines contained in this circular apply to all merchant marine physical examinations and should be provided to medical personnel for use in conjunction with the physical examination form (CG-719K or equivalent).

b. All RECs should use this circular as a guide when evaluating physical examination results submitted by mariners in accordance with Title 46, CFR, Parts 10, 12, and 13.

1. The physical standards in this enclosure apply to an applicant for an original license as a deck officer, engineer officer, or pilot. The same standards apply to the upgrade or renewal of these licenses unless specifically noted.

2. An applicant for either issuance of an original Merchant Mariner Document (MMD) or renewal of an MMD must also meet physical standards. With the exception of an MMD for the entry level ratings, the standards are the same ones that apply to issuance of a license.

These standards are summarized below:

a. ORIGINAL MMD ENDORSED AS ORDINARY SEAMAN, WIPER, STEWARDS DEPARTMENT FOOD HANDLER

No physical required; however, applicants should have the agility, strength, and flexibility to:

1. Climb steep or vertical ladders

2. Maintain balance on a moving deck

3. Pull heavy fire hoses up to 400 feet and have the ability to lift fully charged fire hoses

4. Rapidly don an exposure suit

5. Step over door sills of 24 inches in height

6. Open or close watertight doors that may weigh up to 56 pounds
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<table>
<tr><th>Condition</th><th>FAA
(all classes of airmen)</th><th>Railroad†</th><th>Merchant Mariner‡</th></tr>
<tr>
<td></td>
<td>
Aerospace Medical Dispositions
Item 46. Neurologic - Extrapyramidal, Hereditary, and Degenerative Diseases of the Nervous System[18]
<table>
<tr><th>Disease/ Condition</th><th>Class</th><th>Evaluation Data</th><th>Disposition</th></tr>
<tr><td>Dystonia Musculorum Deformans;

Huntington's Disease;

Parkinson's Disease;

Wilson's Disease; or

Gilles de la Tourette Syndrome;

Alzheimer's Disease;
Dementia (unspecified);

or

Slow viral diseases
i.e., Creutzfeldt
Jakob's Disease</td><td>All</td><td>Obtain medical records and current neurological status, complete neurological evaluation with appropriate laboratory and imaging studies, as indicated

May consider Neuro-psychological testing</td><td>Requires FAA Decision</td></tr>
</table>
[18] Extrapyramidal, Hereditary, and Degenerative Diseases of the Nervous System: Considerable variability exists in the severity of involvement, rate of progression, and treatment of the above conditions. A complete neurological evaluation with appropriate laboratory and imaging studies, including information regarding the specific neurological condition, will be necessary for determination of eligibility for medical certification.
http://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/app_process/exam
</td>
<td></td>
<td>
b. MMD ENDORSED AS ABLE SEAMAN
Same physical requirements that apply to deck officer's licenses.
c. RENEWAL OF MMD ENDORSED AS ABLE SEAMAN
Same physical requirements for renewal of a deck officer's license.
d. MMD ENDORSED AS QMED OR TANKERMAN
Same requirements for original engineer's license. If the applicant has an unexpired engineer's license the physical exam may be waived.
e. RENEWAL OF MMD ENDORSED AS QMED OR TANKERMAN
Same physical requirements for renewal of an engineer's license.
http://www.uscg.mil/hq/g-m/nvic/2_98/n2-98.pdf
Potentially disqualifying conditions listed in the Physical Evaluation Guidelines for Merchant Mariner's Documents and Licenses included any disease or constitutional defect which would result in gradual deterioration of performance of duties, sudden incapacitation or otherwise compromise shipboard safety, including required response in an emergency situation. Neurologic guidelines and standards include the following:
NEUROLOGIC
Any convulsive disorder resulting in an altered state of consciousness regardless of control by medication requires further evaluation.
Any condition which seriously limits balance or coordination (e.g., Parkinson's disease, chorea, Meniere's disease).
Chronic organic/traumatic brain syndrome
Neurosyphilis
Narcolepsy
Senility
Somnambulism
</td>
</tr>
</table>

Condition	FAA (all classes of airmen)	Railroad†	Merchant Mariner‡
	Guide for Aviation Medical Examiners **Application Process for Medical Certification** **Applicant History - Item 18. Medical History** **I. Neurological disorders; epilepsy, seizures, stroke, paralysis, etc.** The applicant should provide history and treatment, pertinent medical records, current status report and medication. The Examiner should obtain details about such a history and report the results. An established diagnosis of epilepsy, a transient loss of control of nervous system function(s), or a disturbance of consciousness is a basis for denial no matter how remote the history. Like all other conditions of aeromedical concern, the history surrounding the event is crucial. Certification is possible if a satisfactory explanation can be established. (See Item 46). http://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/app_process/app_history/item18/l/index.cfm?print=go **Examination Techniques** **Item 46. Neurologic** A neurologic evaluation should consist of a thorough review of the applicant's history prior to the neurological examination. The Examiner should specifically inquire concerning a history of weakness or paralysis, disturbance of sensation, loss of coordination, or loss of bowel or bladder control. Certain laboratory studies, such as scans and imaging procedures of the head or spine, electroencephalograms, or spinal paracentesis may suggest significant medical history. The Examiner should note conditions identified in Item 60 on the application with facts, such as dates, frequency, and severity of occurrence. A history of simple headaches without sequela is not disqualifying. Some require only temporary disqualification during periods when the headaches are likely to occur or require treatment. Other types of headaches may preclude certification by the Examiner and require special evaluation and consideration (e.g., migraine and cluster headaches). One or two episodes of dizziness or even fainting may not be disqualifying. For example, dizziness upon suddenly arising when ill is not a true dysfunction. Likewise, the orthostatic faint associated with moderate anemia is no threat to		

Condition	FAA (all classes of airmen)	Railroad†	Merchant Mariner‡
	aviation safety as long as the individual is temporarily disqualified until the anemia is corrected. An unexplained disturbance of consciousness is disqualifying under the medical standards. Because a disturbance of consciousness may be expected to be totally incapacitating, individuals with such histories pose a high risk to safety and must be denied or deferred by the Examiner. If the cause of the disturbance is explained and a loss of consciousness is not likely to recur, then medical certification may be possible. The basic neurological examination consists of an examination of the 12 cranial nerves, motor strength, superficial reflexes, deep tendon reflexes, sensation, coordination, mental status, and includes the Babinski reflex and Romberg sign. The Examiner should be aware of any asymmetry in responses because this may be evidence of mild or early abnormalities. The Examiner should evaluate the visual field by direct confrontation or, preferably, by one of the perimetry procedures, especially if there is a suggestion of neurological deficiency. http://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/app_process/exam_tech/item46/et/ **Medical Certification Standards and Procedures Training (MCSPT) used as correspondence for AME's and Staff include:** **Item 18l: Neurological disorders; epilepsy, seizures, stroke, paralysis, etc.** Diagnosis of Epilepsy or seizures is cause for disqualification no matter how remote the history. Applicants with a history of Epilepsy MUST be medication and seizure free for 10 years before they can be considered for Special Issuance. Neurological conditions that may incapacitate MUST be deferred. Other neurological conditions that may cause sudden incapacitation (other than seizure) are: 1. Multiple Sclerosis. 2. Myasthenia Gravis. 3. Muscular Dystrophy 4. Central nervous system tumors that affect neurologic functions.		

Condition	FAA (all classes of airmen)	Railroad†	Merchant Mariner‡
	Generally Transient Ischemic Attacks (TIAs), strokes, Transient Global Amnesia, and Reversible Ischemic Neurological Defects, require a two-year recovery period. Seizures (other than Epilepsy) may require 2, 5, or 10-year recovery periods, seizure-free, off medication before an applicant can be considered for medical certification.		

* Source of information for FAA Regulations and Guidelines:
http://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/special_iss/all_classes/glaucoma/
http://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/app_process/exam_tech/item52/amd/
http://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/app_process/exam_tech/item50/amd/

† 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://www.uscg.mil/hq/g-m/nvic/2_98/n2-98.pdf

Regulatory Medical Fitness Standards in Various Countries

The effect of neurological disorders and impairments on CMV driving is widespread. Various countries globally have established regulatory medical fitness standards for the protection and safety of the public interest, including licensed drivers. The medical standards of these countries are used to assess and determine the fitness of drivers operating CMVs. Likewise, neurological disorders are defined, and criteria for establishing these standards are constructed. Each country demonstrates its interpretation of neurological disorders through definition and by determining the individuals who would be affected.

Regulatory Standards in Select Countries

Regulatory standards and guidelines pertaining to neurological disorders and CMV driving in select countries worldwide (Canada, Australia, the United Kingdom, and Sweden) are presented in Table 12. Each country has specific standards for driving eligibility of individuals with PD or MS, although there is some slight variability in the restrictions. In general, these countries require following individuals with PD or MS closely (assuming their condition is mild enough to pass an initial evaluation) with intermittent review/reevaluation to determine whether driving should be discontinued. These countries do not appear to provide separate standards for private and commercial motor vehicle driving.

Table 12. Worldwide Guidelines for CMV Drivers with Multiple Sclerosis/Parkinson's Disease

Country	Reference	General
Canada	Determining Medical Fitness to Operate Motor Vehicles. CMA (Canadian Medical Association) Driver's Guide 7th edition. (2006)	Loss of muscle strength or coordination occurs in a wide variety of disorders, each of which poses a special problem. This includes such conditions as weakness, altered muscle tone, involuntary movements or reduced coordination due to poliomyelitis, Parkinson's disease, multiple sclerosis, cerebral palsy… In the early stages of these conditions, no driving restrictions may be necessary. However, in serious cases, it will be immediately obvious that the applicant is unable to drive safely. When the condition is progressive or there are multiple medical conditions, the patient must be followed closely and driving discontinued when the disability reaches a point that makes driving unsafe. In such conditions, the physician should recommend a functional evaluation if the patient wishes to resume driving.
Australia	Assessing Fitness to Drive (For Commercial and Private Vehicle Drivers) Medical Standards for Licensing and Clinical Management Guidelines. Austroads and NTC (National Transport Commission) Australia (2006)	The criteria for an *unconditional license* are NOT met: ○ If the person has Parkinsonism, multiple sclerosis, degenerative peripheral neuropathy, progressive muscular dystrophy or any other severe neuromuscular disorder. A *conditional license* may be granted by the Driver Licensing Authority, taking into account the opinion of a neurologist or rehabilitation specialist, and the nature of the driving task, and subject to at least annual review, if the disability is limited to minor effects on driving, taking into account: ○ Response to treatments; ○ Report of a driver assessor, and ○ Modifications to the vehicle.
United Kingdom	At a Glance Guide to the current Medical Standards of Fitness to Drive (for Medical Practitioners) Issued by Drivers Medical Group. DVLA, Swansea (February 2007)	Chronic Neurological Disorders (i.e., Parkinson's disease and multiple sclerosis): refusal or revocation if condition is progressive or disabling. If driving would not be impaired and condition stable, can be considered for licensing subject to satisfactory reports and annual review.
Sweden	Swedish National Road Administration Statute Book Effective 1/1/99	Possession ○ Diseases in the nervous system which imply a danger to traffic safety constitute grounds for denial of possession. ○ The risk assessment shall take into consideration the clinical

Country	Reference	General
		state and development as well as the results of treatment. In this connection, due consideration shall be given to the presence of motor or sensory symptoms that affect balance, co-ordination or psychomotor speed as well as defects of a cognitive nature. ○ Due consideration should be given to CMV drivers, given the additional risks and dangers to traffic safety involved in such possession. Reappraisal ○ In the case of progressive diseases such as Parkinson's disease, multiple sclerosis or any other neurodegenerative disease, a reappraisal shall occur at intervals considered suitable in each individual case.

Methods

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

Key Questions

This evidence report addresses six key questions. Each of these key questions was developed by the FMCSA such that the answers to these questions provided information that would be useful in updating their current medical examination guidelines. The five key questions addressed in this evidence report are as follows:

Key Question 1: What are the criteria that define when an individual with Parkinson's Disease should stop driving a CMV?

Key Question 2: What is the impact of pharmacotherapy for PD on driver safety?

Key Question 3: Are individuals with Multiple Sclerosis (MS) at an increased risk for a motor vehicle crash? If so, what factors associated with MS are predictive of an increased crash risk?

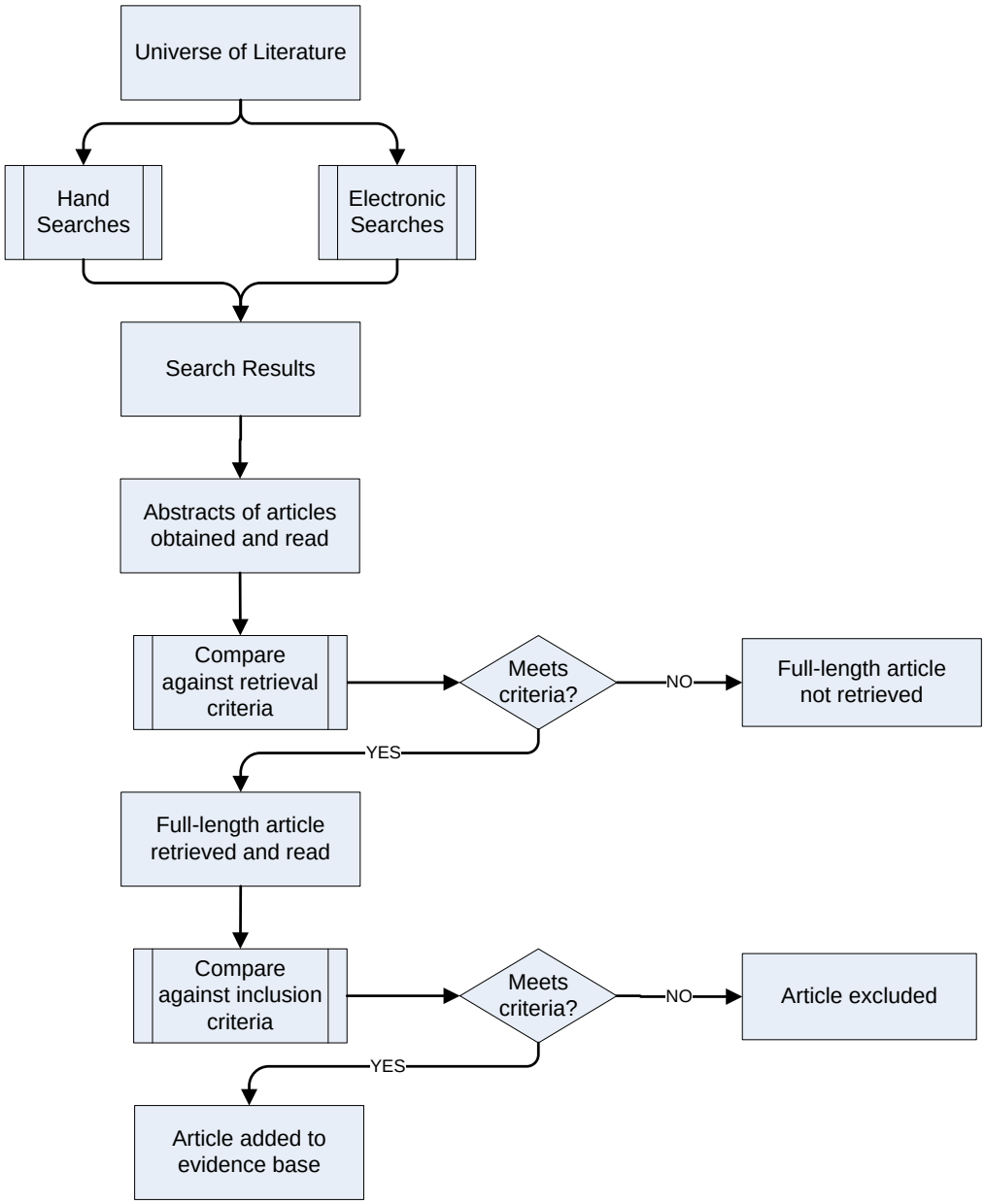
Key Question 4: How frequently should an individual with MS be assessed in order to monitor whether they remain safe to drive?

Key Question 5: What is the impact of pharmacotherapy for MS on driver safety?

Identification of Evidence Bases

The individual evidence bases for each of the five key questions addressed in this evidence report were identified using the multistage process captured by the algorithm presented in Figure 15. 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 15. 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. Full details of the search strategies used in this report are presented in Appendix A.

Electronic Searches

We performed comprehensive searches of the electronic databases listed in Table 13.

Table 13. Electronic Databases Searched

Name	Date Limits	Platform/Provider
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	1982 through April 23, 2008	OVID
The Cochrane Central Register of Controlled Trials (CENTRAL)	Through 2008, Issue 2	www.thecochranelibrary.com
The Cochrane Database of Methodology Reviews (Methodology Reviews)	Through 2008, Issue 2	www.thecochranelibrary.com
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	Through 2008, Issue 2	www.thecochranelibrary.com
Database of Abstracts of Reviews of Effects (DARE)	Through 2008, Issue 2	www.thecochranelibrary.com
EMBASE (Excerpta Medica)	1980 through April 23, 2008	OVID
Health Technology Assessment Database (HTA)	Through 2008, Issue 2	www.thecochranelibrary.com
MEDLINE	1950 through April 23, 2008	OVID
PreMEDLINE	Searched April 23, 2008	OVID
PsycINFO	Through April 23, 2008	OVID
TRIS	Searched December 11, 2007	
U.K. National Health Service Economic Evaluation Database (NHS EED)	Through 2008, Issue 2	www.thecochranelibrary.com
U.S. National Guideline Clearinghouse™ (NGC)	Searched December 17, 2007	www.ngc.gov

Manual Searches

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

Retrieval Criteria

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

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

Inclusion and Exclusion Criteria

Each retrieved article was read in full by an ECRI Institute 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.(62) 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 considered 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., "sleepiness associated with pharmacotherapy in individuals with PD may affect driver safety") and a quantitative conclusion (e.g., "the odds ratio of sleepiness associated with pharmacotherapy for PD is X"). As shown in Table 14, we assigned a separate strength-of-evidence rating to each of type of conclusion. Evidence underpinning a qualitative conclusion was rated according to its strength, and evidence underpinning quantitative conclusions was rated according to the stability of the effect size estimate that was calculated.

Table 14. Strength of Evidence Ratings for Qualitative and Quantitative Conclusions

Strength of Evidence	Interpretation
Qualitative Conclusion	
Strong	Evidence supporting the qualitative conclusion is convincing. It is highly unlikely that new evidence will lead to a change in this conclusion.
Moderate	Evidence supporting the qualitative conclusion is somewhat convincing. There is a small chance that new evidence will overturn or strengthen our conclusion. ECRI Institute recommends regular monitoring of the relevant literature for moderate-strength conclusions.
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. ECRI Institute recommends frequent monitoring of the relevant literature.
Insufficient	Although some evidence exists, the evidence is insufficient to warrant drawing an evidence-based conclusion. ECRI Institute recommends frequent monitoring of the relevant literature.

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

The definitions presented in the table above are intuitive. Qualitative conclusions that are supported by strong evidence are less likely to be overturned by the publication of new data than conclusions supported by weak evidence. Likewise, quantitative effect size estimates 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, random-effects meta-analyses were used to pool data from different studies.(63-72) Important differences in the findings of different studies (heterogeneity) were identified using the Q-statistic and I^2.(68,73-78) Whenever appropriate, heterogeneity was explored using meta-regression techniques.(79-81) Sensitivity analyses, aimed at testing the robustness of our findings, were performed using cumulative random-effects meta-analyses.(82-88) All meta-analyses in this Evidence Report were performed using Comprehensive Meta-Analysis software.(89-91)

We calculated several different estimates of effect. The choice of effect size estimate depended on the purpose of the studies we assessed, their design, and whether reported outcome data were continuous or dichotomous. 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). Time-to-event data were analyzed using the hazard ratio (HR). The formulae for these effect sizes and their variance are presented in Table 15. If means and standard deviations were not available for continuous data, every effort was made to determine an estimate of treatment effect from reported statistics (e.g., t-values, f-values) or from p-values using methods described in detail elsewhere.(92)

Table 15. Effect Size Estimates Used in Evidence Report and their Variance

Effect Size	Formula (Effect Size)	Formula (Variance)
WMD	$\mu_{TG} - \mu_{CG}$	$\left(\sqrt{\frac{(n_{TG}-1)(s_{TG})^2 + (n_{CG}-1)(s_{CG})^2}{n_{TG}+n_{CG}-2}}\right)\left(\frac{1}{n_{TG}} + \frac{1}{n_{cg}}\right)$
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)		
Event Rate	$a/a+b$	$\ln\left[\frac{1}{a} + \frac{1}{a+b}\right]$
Where: a = number of individuals in cohort experiencing an event; b = number of individuals in cohort who did not experience an event		
RR (incidence)	$\left(\frac{a_{msd}}{pt_{msd}}\right) \Big/ \left(\frac{b_{control}}{pt_{control}}\right)$	$\ln\left[\frac{1}{a_{msd}} + \frac{1}{b_{control}}\right]$
Where: a = number of individuals with disorder/who crashed; pt_{msd} = rate denominator (disorder grp); b = number of individuals without disorder/who crashed; $pt_{control}$ = rate denominator (control grp)		
OR	$\left(\frac{a}{b}\right) \Big/ \left(\frac{c}{d}\right) = \left(\frac{ad}{bc}\right)$	$\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}$
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.		
HR	$\frac{O_{pi}/E_{pi}}{O_{ci}/E_{ci}}$	$\exp\left(\ln\left[\frac{1}{E_{pi}} + \frac{1}{E_{ci}}\right]\right)$
Where O_{pi} = observed number of events in treatment group; O_{ci} = observed number of events in control group; E_{pi} = log rank expected number of events in treatment group; E_{ci} = log rank expected number of events in control group		

HR = Hazard ratio
OR = Odds Ratio
RR = Rate ratio
SMD = Standardized mean difference
WMD = Weighted 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: What criteria define when an individual with Parkinson's disease (PD) should stop driving a CMV?

Introduction

PD is a common neurological disorder that is progressive, neurodegenerative, and associated with a loss of dopaminergic nigrostriatal neurons.(93) Prevalence in the United States is estimated to be approximately 500,000 at an incidence rate of 13 per 100,000 per year.(48,94) The disease is commonly found in individuals approximately 60 years of age with both prevalence and incidence rates increasing with age.

Assessing Severity of Parkinson's Disease

UPDRS is the most widely used scale to measure disease progression in patients with PD. Allotment of scores is based on patient interview and physical exam and encompasses four subscales of assessment: (I) cognition, behavior, and mood; (II) activities of daily living; (III) motor performance; and (IV) complications of therapy. UPDRS motor assessment has been suggested as an indicator of fitness to drive with a 25% reduction representing a clinically relevant improvement.(95) Symptom severity can also be evaluated by the five-stage Hoehn and Yahr Scale. The Schwab and England scale evaluates activities of daily living ranging from 100% (completely independent) to 0% (vegetative state). A comparison of these scales can be found in Table 16.(39-41,96) Patients with severe/advanced disability on these scales are unlikely to be considered fit to drive a motor vehicle.

Table 16. Comparison of PD Diagnostic Scales

Scale	Score	Signs and Symptoms	Outcome
Unified Parkinson Disease Rating Scale (UPDRS)	0 (none), 1 (mild), 2 (moderate), 3 (severe), 4 (chronic)	*Mentation, Behavior, Mood*: Intellectual impairment; thought disorder; depression; motivation/initiative *Activities of Daily Living*: Speech, salivation, swallowing, handwriting, cutting food/handling utensils, dressing, hygiene, turning in bed/adjusting bed clothes, falling-unrelated to freezing, freezing when walking, walking, tremor, sensory complaints related to parkinsonism *Motor Exam*: Speech, facial expression, tremor at rest, action or postural tremor, rigidity, finger taps, hand movements, rapid alternating movements; leg agility, arising from chair, posture, gait, postural stability, body bradykinesia/hypokinesia *Complications of Therapy (in the past week)*- dyskinesias, clinical fluctuations, other complications	0 (no disability) – 199 (total disability)
Hoehn and Yahr		Unilateral; mild; inconvenient but not disabling; usually presenting with tremor of one limb; noticeable changes in posture, locomotion and facial expression	1
		Bilateral; minimal disability; affects posture and gait	2

Scale	Score	Signs and Symptoms	Outcome
		Significant slowing of body movements; impairment of equilibrium with walking/standing; overall moderately severe dysfunction	3
		Severe symptoms; limited walking; rigidity and bradykinesia; unable to live alone; more pronounced tremor	4
		Cachectic stage; cannot stand/walk; need continual nursing care	5
Schwab and England Activities of Daily Living Scale	100%	Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.	Completely independent.
	90%	Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.	Completely independent.
	80%	Takes twice as long. Conscious of difficulty and slowness.	Completely independent in most chores.
	70%	More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.	Not completely independent.
	60%	Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.	Some dependency.
	50%	Help with half, slower, etc. Difficulty with everything.	More dependent.
	40%	Can assist with all chores, but few alone.	Very dependent.
	30%	With effort, now and then does a few chores alone or begins alone.	Much help needed.
	20%	Severe invalid.	Can be a slight help with some chores.
	10%	Complete invalid.	Totally dependent, helpless.
	0%	Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.	Vegetative.

Identification of Evidence Base

The evidence base identification pathway for Key Question 1 is summarized in Figure 16. Our searches[2] identified a total of 92 articles that were potentially relevant to this key question. Following application of the retrieval criteria for this question (Appendix D), 34 full-length articles were retrieved and read in full. Fifteen of these retrieved articles were found to meet the inclusion criteria (Appendix D) for this key question. Of these 15, there was one group of three studies and two groups of two studies that were "sister" publications which shared all or most of the same patients. Due to patient overlap, they are grouped together in Table 17. The 15 studies therefore represent 11 non-overlapping patient groups. Despite the patient overlap, each study provided unique data on outcomes and variables that may affect the outcomes. Table D-1 of Appendix D lists the 19 articles that were retrieved, read in full, and then excluded. The table also provides justification for their exclusion.

[2] See Appendix A for search strategies.

Figure 16. Development of Evidence Base for Key Question 1

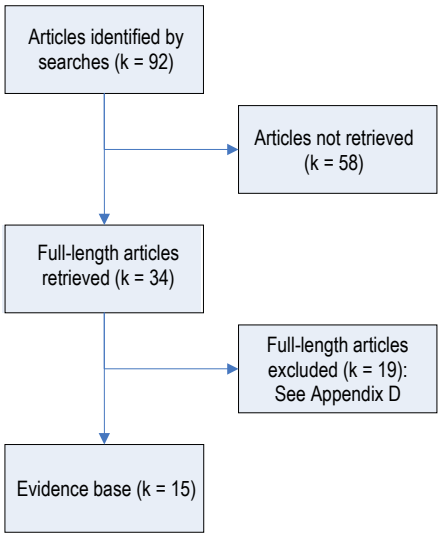


Table 17. Evidence Base for Key Question 1

Reference	Year	Study Location	Country
Crash Studies			
Meindorfner(97)	2005	Wurzburg	Germany
Adler et al.(98)	2000	Minnesota	USA
Dubinsky et al.(99)	1991	Kansas	USA
Excessive Daytime Sleepiness Studies			
Hobson et al.(100)	2002	NR	Canada
Driving Performance Studies			
Devos et al.(101)	2007	Brussels	Belgium
Singh et al.(102)	2007	Edinburgh	U.K.
Uc et al.(103-105) *	2007, 2006	Iowa	USA
Stolwyk et al.(106,107) *	2006	Melbourne	Australia
Worringham et al.(108) Wood et al.(109) *	2005	Queensland	Australia
Zesiewicz et. al.(110)	2002	Florida	USA
Heikkila et al.(111)	1998	Oulu	Finland

NR = Not Reported
* Studies that were concluded to be "sister" publications (sharing all or most of the same patients) based upon information provided and therefore grouped together.

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

Three crash studies, one study of excessive daytime sleepiness, and 11 driving performance studies met the inclusion criteria for this question. These observational studies varied in study design (14 cohort, one

survey), how the disorder was confirmed, and whether the outcome was self-reported. However, all of the included studies performed similar comparisons (individuals with PD versus no PD). None of the studies reported controlling for driving exposure. The primary characteristics of the 15 included studies that address Key Question 1 are presented in Table 18 below.

Table 18. Key Study Design Characteristics of Studies that Address Key Question 1

Reference	Year	Study Design	Comparison	How was PD Defined (e.g., Disease Stage by H&Y Scale, UPDRS Score)?	PD Clinically Confirmed?	Factors Controlled for (if compared to non PD)?	Driving Exposure Controlled for?	Primary Outcome	Definition of Crash	Outcome Self-reported?
Crash Studies										
Meindorfner(97)	2005	Survey£	N/A. Assessed SOS and driving behavior in study group	Combined H&Y Stage	No. Self-report	No	No	Driving Mobility	Crashes in past 5 years	Yes
Adler et al.(98)	2000	Cohort†	PD vs. no PD	NR	NR	Yes. Age, education, gender, residence	No	Driving patterns (historical and current), including crash history	Past 5-year crash history	Yes
Dubinsky et al.(99)	1991	Cohort†	PD vs. no PD	H&Y Stage	Yes. Testing	No	No	Crash	Lifetime number of crashes	Yes
Excessive Daytime Sleepiness Studies										
Hobson et al.(100)	2002	Cohort†	Sudden Onset of Sleep vs. No Sudden Onset of Sleep	High function PD; H&Y Stage; Clinical diagnosis with no cognitive impairment; medication working	Yes. Clinical diagnosis	No	No	Excessive daytime sleepiness	N/A	Yes
Driving Performance Studies										
Devos et al.(101)	2007	Cohort†	PD vs. no PD	H&Y Stage	Yes.UK Brain Bank Diagnostic Criteria	Yes. Age and gender	No	Fitness to drive	Simulated on-road/off-road crash, traffic cone hits, pedestrian hits	No
Singh et al.(102)	2007	Cohort†	Suitable to Drive vs. Not Suitable to Drive	H&Y Stage	Yes	No	No	Driving ability	N/A	No
Uc et al.(103-105) *	2007, 2006	Cohort†	PD vs. no PD	H&Y score	Yes. Clinician assessment	Yes. Age, driving exposure, years of education	Yes (miles/week)	Driving performance	N/A	No

Reference	Year	Study Design	Comparison	How was PD Defined (e.g., Disease Stage by H&Y Scale, UPDRS Score)?	PD Clinically Confirmed?	Factors Controlled for (if compared to non PD)?	Driving Exposure Controlled for?	Primary Outcome	Definition of Crash	Outcome Self-reported?
Stolwyk et al.(106,107) *	2006, 2005	Cohort†	PD vs. no PD	Medical assessment with no other neurological impairments	Yes. Clinician assessment	NR	NR	Driving performance	N/A	No
Worringham et al.(108) Wood et al.(109) *	2005	Cohort†	PD vs. no PD	H&Y Stage; UPDRS Rating	Yes. Clinician assessment	Yes. Age.	No	Driving Safety Prediction	N/A	No
Zesiewicz et. al.(110)	2002	Cohort†	PD vs. no PD	H&Y Stage; UPDRS Rating	Yes. Testing; pharmacotherapy response	No	No	Simulator Crash	1 or more simulator crashes during study period	No
Heikkila et al.(111)	1998	Cohort†	PD vs. no PD	H&Y Stage	Yes. Clinician assessment	Yes, Age	NR	Driving performance	N/A	No

H&Y = Hoehn & Yahr Scale
N/A = Not Applicable
NR = Not Reported
PD = Parkinson's disease
SOS = Sudden Onset of Sleepiness
UPDRS = Unified Parkinson's Disease Rating Scale

† A cohort study in which individuals are followed over a time period to determine development of the outcome.
£ A survey study in which the study group is defined according to response of presence of sudden onset of sleepiness and driving behavior.
* Studies that were concluded to be "sister" publications (sharing all or most of the same patients) based upon information provided and therefore grouped together.

Quality of Evidence Base

The findings of our quality assessment of the included studies composing the evidence base for Key Question 1 are summarized in Table 19. Although observational studies often statistically adjust for known confounding factors, only random allocation can control for unknown confounding. Therefore, the quality rating of the cohort and survey studies can never be high. The cohorts within each study were relatively comparable. The crash and daytime sleepiness study quality scores were both weakened by using self-reported outcome data. Among driving performance studies, nine out of 11 studies scored moderate as outcome data were more objective (i.e. did not rely upon the participant's memory for outcome measurement). The quality assessment instruments are shown in Appendix F.

Complete details of our quality assessment can be found in the study summary tables presented in Appendix G. Our analysis concluded that the quality of all of the included studies was low to moderate.

Table 19. Quality of the Studies That Assess Key Question 1

Reference	Year	Quality Scale Used	Quality
Crash Studies			
Meindorfner(97)	2005	ECRI Institute Quality Scale VI: Surveys	Low
Adler et al.(98)	2000	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Low
Dubinsky et al.(99)	1991	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Low
Excessive Daytime Sleepiness Studies			
Hobson et al.(100)	2002	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Low
Driving Performance Studies			
Devos et al.(101)	2007	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Singh et al.(102)	2007	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Uc et al.(103-105)	2007, 2006	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Stolwyk et al.(106,107)	2006, 2005	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Worringham et al.(108) Wood et al.(109)	2005	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Zesiewicz et. al.(110)	2002	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Low
Heikkila et al.(111)	1998	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Low

Generalizability of Evidence to Target Population

The purpose of this subsection is to provide details of the extent to which individuals enrolled in the studies that address Key Question 1 are similar to CMV drivers in the United States. The generalizability of the findings of the included studies to CMV drivers is unclear as none of the included studies examined PD among CMV drivers. CMV drivers have greater risk exposure because they spend more time driving than non-CMV drivers. Further, the mean age of study enrollees was older (mean age range 59 to 72.7) than the average in the CMV driver population. Also, women were overrepresented in these studies relative to the CMV driver population. Important characteristics of the individuals included in the studies that address Key Question 1 are presented in Table 20 below.

Table 20. Generalizability of Studies that Address Key Question 1

Reference	Year	Number of Individuals with-PD Included (n =)	Diagnosis (PD)	PD Disease Stage (e.g., mild, moderate, severe)	Mean Duration Years of PD (SD)	% Drivers with PD	Age Distribution (SD) **	% Male	% CMV Drivers	Driving Exposure (i.e., average miles driven annually)	Driving Conditions (e.g., night driving, driving alone)	Generalizability to Target Population?
Crash Studies												
Meindorfner(97)	2005	6.620	Self-reported	Modified H&Y Stages (minor, moderate, significant)	9.4 (6.7)	60	68.5 (8.7)	59.9	0	7,668.6 km	NR	Unclear
Adler et al.(98)	2000	89	Self reported	PD with or without medication & with or without movement restriction; poor to excellent health	NR	100 (PD only); 17.38 (combined w/ control)	72.7 (NR)	56 (PD only)	0	54.9 average years driving; 4.6 average days of driving per week	NR	Unclear
Dubinsky et al.(99)	1991	150	Clinic records	Varied (H&Y score 1-3)	Varied (4.95-10.5 based upon stage)	60	67.8 (8.8)	NR	0	583.0 ±627.0 miles/month	Employment driving (18%)*; Errand driving (46.5%)*; Pleasure driving (34.5%)*	Unclear
Excessive Daytime Sleepiness Studies												
Hobson et al.(100)	2002	638	Clinician diagnosis	NR. Highly functional PD with H& Y mean score of 2.2 [SD = 0.7]	8.1 (5.4) [all] 7.2 (4.9) [drivers only- n = 420]	65.8*	65.7(10.6)	53% (total population) 73% (drivers only-n = 420)	0	NR	NR	Unclear
Driving Performance Studies												
Devos et al.(101)	2007	40	UK Brain Bank Diagnostic Criteria	H &Y Stage score 1-3	6.7 (4.0)	50	61.6 (9.4)	82.5 (PD only)	0	NR	NR	Unclear

Reference	Year	Number of Individuals with-PD Included (n =)	Diagnosis (PD)	PD Disease Stage (e.g., mild, moderate, severe)	Mean Duration Years of PD (SD)	% Drivers with PD	Age Distribution (SD) **	% Male	% CMV Drivers	Driving Exposure (i.e., average miles driven annually)	Driving Conditions (e.g., night driving, driving alone)	Generalizability to Target Population?
Singh et al.(102)	2007	154	Clinician diagnosis	H&Y Stage score 1-3	5.9 (NR)	100	67.6 (NR)	87*	0	42.1 years driving	On-road	Unclear
Uc et al.(103-105) [a]	2007, 2006	79[b]	Clinician diagnosis	Mild to Moderate Stage of PD	5.6 (5.0)[c]	100	65.9 (8.6)	59* (all) 81* (PD only)	0	171.3±172.3 miles/week	On-road day driving	Unclear
Stolwyk et al.(106,107) [a]	2006, 2005	18	Clinician diagnosis	Mild to Moderate Stage of PD	6.67 (4.21)	100	67.62 (6.53)	70	0	46.72 years driving Average weekly driving distance (PD group): 5-50 km 39% 50-200km 44% >200km 17%	Simulated two-lane open road way	Unclear
Worringham(108) Wood et al.(109) [a]	2005	25	Clinician diagnosis	H&Y Stage score 2 (median)	6.2 (4.6)	100	63.7 (6.8)	84 (PD only)	0	NR	On-road	Unclear
Zesiewicz et. al.(110)	2002	39	Pharmaco-therapy response; clinician diagnosed	Varied (H&Y score 1-4)	NR	60	63.8 (11.5)	64.1* (PD only)	0	401 ±509.0 miles/month	Day and night driving	Unclear
Heikkila et al.(111)	1998	20	Clinician diagnosis	Mild to Moderate Stage of PD	5.6 (2.8)	100	59 (11)	100	0	2.6[d] (0.7) km travelled in past year (mean/SD); 984 (829) total driving (1000km)	On-road (urban and suburban surrounding) standard and relatively complex route	Unclear

H&Y = Hoehn and Yahr
NR = Not Reported
PD = Parkinson's disease

* Calculated by ECRI Institute from reported data.
** Years of age for Individuals with Parkinson's disease with and without the primary outcome only from Table 18 (e.g., crash)
[a] Studies that were concluded to be "sister" publications (sharing all or most of the same patients) based upon information provided and therefore grouped together.
[b] The highest "n" among the sister studies is included.
[c] These numbers varied slightly among the three studies by Uc et al. , due to slight differences in the number of patients in each study. This was the mean duration reported in the largest study.
[d] According to the authors categories 2= 5000-10,000km and 3= 10,000-30,000km therefore the mean value of 2.6 is equivalent to between 5000-30,000 km travelled

Findings

Of the studies that met the inclusion criteria for Key Question 1, three studies provided direct evidence of crash risk with noncommercial drivers.(97-99) These studies provided actual and self-reported crash data from which crash risk could be determined in relation to various risk factors in drivers with PD. The remaining 12 studies evaluated indirect outcomes (sleep while driving, driving simulator crash and driving fitness/performance), which may or may not be associated with crash risk.(100-102,106,108,110) These studies identified certain risk factors that predicted falling asleep while driving, driving test failure, or decreased performance of specific driving tasks among individuals with PD. All studies varied in study design and sample size, though comparable in PD definition (when reported) as previously provided in Table 18.

Impact of PD-associated Factors on Crash Risk

Direct Evidence

Table 21 shows findings from a survey study assessing driving behavior and sudden onset of sleepiness among individuals with PD. Univariate analysis was performed using explanatory variables which include disease severity, sudden onset of sleepiness, and driving exposure (kilometers driven per year). Each included variable correlated with crash involvement. However, if multiple regression analysis had been conducted, the possibility exists that some variables might no longer be significantly correlated with crash due to the potential association of the included variables. Thus, these findings need to be replicated to allow a definitive conclusion.

Table 21. Crash Involvement Findings in Drivers with PD

Reference	Year	Crash Data		
		Explanatory Variables	Odds Ratio (95% CI)	Evidence of Increased Crash Risk?
Meindorfner et al.(97)	2005	Moderate (vs. minor) disease severity	1.42 (1.12-1.81)	Yes. p <0.005
		Advanced (vs. minor) disease severity	1.51 (1.05-2.18)	Yes. p <0.050
		Sudden onset of sleep (SOS) at the wheel	3.16 (2.33-4.30)	Yes. p <0.001
		Km per year ≥ (vs. <) 6,000	1.49 (1.18-1.88)	Yes. p <0.005

The study by Dubinsky et al. compared crash rates of patients with PD by Hoehn & Yahr Stage to the crash rate of healthy controls (Table 22).(99) Statistical significance was reported for Hoehn and Yahr Stages 2 and 3, indicating an increased crash risk among patients at these stages of PD. No evidence of increased crash risk was found among patients in Hoehn and Yahr Stage 1. However, this study did not perform multivariate analysis to adjust for the potential effects of other variables, so the true impact of disease stage on crash risk remains uncertain. Therefore, these findings need to be replicated to allow a definitive conclusion.

Table 22. Crash Rate Findings for Drivers with PD—Hoehn and Yahr Level Designated

Reference	Year	Crash Rate Data**			
		PD Drivers Crash Rate (number still driving)	Normal Controls Crash Rate (number still driving)	Rate Ratio* (95% CI)	Evidence of Increased Crash Risk?
Crash (past 3 years)					
Dubinsky et al.(99)	1991	**H&Y Stage 1**			
		0.056 (42)	0.115 (98)	0.487 (0.119-1.985)	No. p = 0.315
		H&Y Stage 2			
		0.384 (50)	0.115 (98)	3.339 (1.600-6.967)	Yes. p = 0.001
		H&Y Stage 3			
		0.373 (25)	0.115 (98)	3.240 (1.360-7.717)	Yes. p = 0.008

H&Y = Hoehn and Yahr
* The rate of PD with H&Y stage drivers having experienced a motor vehicle crash divided by the rate of normal control population experiencing a crash.
** Calculated by ECRI Institute from reported data.

Table 23 shows the results of a study that compared individuals with PD with movement restriction to individuals with PD without movement restriction.(98) Drivers with PD had a significantly greater risk of crash than neurologically normal drivers (adjusted OR 2.5; 95% CI: 1.4-4.4; p = 0.003). Among drivers with PD, logistic regression analysis found that those with movement restriction were more likely to crash than those without movement restriction (adjusted OR = 3.2; 95% CI: 1.1-9.4; p = 0.034). The study also reported that cognitive impairment was not significantly associated with crash risk. The study's finding suggests that movement restriction may be an important factor to include in criteria that defines when an individual with PD should stop driving. However, this finding needs to be replicated before reaching a definitive conclusion.

Table 23. Crash risk for PD Individuals with Movement Restriction versus PD Individuals without Movement Restriction

Reference	Year	PD Crash with Movement Restriction vs. PD Crash without Movement Restriction				
		All PD with Crash History (total n)	PD Crash With Movement Restriction (n)	PD Crash Without Movement Restriction (n)	Odds Ratio (95% CI)	Evidence of Increased Crash Risk? (p <0.05)
Adler et. al.(98)	2000	32	NR	NR	3.2 (1.1-9.4)	Yes. (p = 0.034)*

NR = Not Reported
* Calculated by ECRI Institute from reported data.

Indirect Evidence

Sleep Attacks While Driving

Table 24 shows the results from a study comparing individuals with PD falling asleep while driving to individuals with PD not falling asleep while driving. A multivariable regression analysis found that scores on two sleep questionnaires (the Epworth Sleepiness Scale [ESS] and the Inappropriate Sleep Composite Score) were significantly associated with falling asleep while driving among individuals with PD (p

<0.001). The ESS presents eight scenarios to rate likelihood of falling asleep: 0 (no chance) to 3 (high chance), with scores of 10 or more indicating daytime sleepiness; it is commonly used and easily administered.(112,113) A number of variables (Hoehn and Yahr score, Mini-Mental State Examination score, leg movements in sleep, anti-Parkinson medication, and use of a sleeping aid) that were significantly associated with falling asleep while driving in a univariate analysis were not found to be significantly associated when tested in the multivariable analysis.

Table 24. Falling Asleep While Driving in PD Drivers

Reference	Year	Variable	Sleep While Driving	
			OR (95% CI)	Evidence of Increased Crash Risk? (p <0.001)
Hobson et. al.(100)	2002	Epworth Sleepiness Scale	1.14 (1.06-1.24)	Yes
		Inappropriate Sleep Composite Score	2.54 (1.76-3.66)	Yes

Driving Performance

Eleven cohort studies attempted to identify variables that predicted driving performance for individuals with PD. Some of these studies shared the same patients, but presented different analyses of the potential association between risk factors and outcomes. Two studies measured drivers with PD classified pass or fail for fitness to drive (based primarily on road tests), one study determined driving suitability based on clinical assessment plus road tests, six studies evaluated performance for specific on-road driving tasks, and two studies evaluated simulated driving performance. The study findings specifically examining driving performance are shown in Tables 25-28.

Although more drivers with PD passed than failed in the study by Devos et al., the fitness-to-drive outcome showed significant correlations with disease duration, self-appraisal of driving fitness, contrast sensitivity, clinical dementia rating (CDR), motor tests and three driving simulator evaluation tasks (Table 25). This is due to individuals with PD who failed the driving performance test scoring significantly worse on these other measures than individuals with PD who passed the driving performance test. Drivers were predicted to pass or fail based upon a formulated assessment, which included contrast sensitivity, CDR, UPDRS III (motor test), and disease duration scores; discriminant function analysis using these four variables correctly classified 90% of subjects with PD who passed or failed the fitness to drive assessment. Addition of TRIP (Test Ride for Investigating Practical fitness to drive) driving simulator scores to the equation increased this percentage to 97.5%.

In Worringham et al., similar pass/fail findings were reported as more drivers with PD passed (n = 13) than failed (n = 12) the driving assessment (Table 25). Those who failed were on average older, with a longer disease duration, and they scored worse on contrast sensitivity, cognitive assessment, and motor function tests compared to individuals who passed the fitness-to-drive assessment. H & Y stage, UPDRS score, and levodopa dosage were not significantly correlated with driving outcome. Discriminant function analysis identified contrast sensitivity (Pelli-Robson test scores), cognitive function (Symbol Digit Modalities test scores), and motor function (Purdue Pegboard test scores) as variables predicting pass or fail on the driving assessment for both patients with PD and controls; an additional variable

(time since diagnosis of PD) improved prediction for the PD group. The resulting equations correctly classified the driving test outcome for 80% of the PD group and 85.7% of the control group. A companion study (Wood et al.) of the same patients assessed the relationship of various clinical factors to driver safety ratings by an occupational therapist and driving instructor. This study found that time since diagnosis had a significant correlation with safety ratings, while H & Y stage, UPDRS score, and levodopa dosage did not.(109)

It is important to note that prediction of driving test outcomes is not the same as prediction of crash risk; patients who failed driving assessments would either not be allowed to drive or at least advised not to drive, depending on the laws of the particular state or country of residence. Thus, they would not be expected to be at risk for motor vehicle crash. Whether the variables identified in these two studies can predict which patients with PD who pass a driving assessment are at increased risk of crash remains to be determined.

Table 25. Assessment of PD Driving Fitness Predictor Variables Comparison Findings (Pass versus Fail)

Reference	Year	Assessment Variables	Driving Performance Data	
			Correlation (r)	p-value
Devos et al.(101)	2007	**Descriptive measures**		
		Disease duration, mean ±SD	0.35(r_b)	p = 0.03
		Self-appraisal of fitness to drive, median (IQR)(↓)	0.47(r_s)	p = 0.002*
		Clinical tests		
		Contrast sensitivity, median(IQR)(↑)	-0.44(r_s)	p = 0.004†
		Cognitive, CDR, median (IQR)(↓)	0.5(r_s)	p = 0.001†
		Motor tests-UPDRS III mean ±SD(↓)	0.5(r_s)	p = 0.001†
		Driving Simulator Evaluation		
		TRIP driving simulator score, median (IQR)(↑)	-0.68(r_s)	p <0.0001‡
		Traffic offenses, median (IQR)(↓)	0.46(r_s)	p = 0.003‡
		Divided Attention-Mean reaction time (IQR)(↓)	0.44(r_b)	p = 0.005‡
Worringham(108)	2005	**Visual Function**		
		Contrast sensitivity (Pelli-Robson)	0.40	p <0.05
		Cognitive		
		Symbol digit modalities	0.46	p <0.005
		Motor Function		
		Purdue Pegboard test	3.59	p <0.005
		Clinical Indices		
		Time since diagnoses (year)	-0.61	p <0.01

ADL = Activities of daily living; CDR = Clinical Dementia Rating; ESS = Epworth Sleepiness Scale; IQR = interquartile range (Q1-Q3); r_b = biserial correlation coefficient; r_{rb} = rank biserial correlation coefficient; r_s = Spearman rank correlation coefficient; SD = Standard Deviation; TRIP = Test Ride for Investigating Practical fitness to drive; UPDRS = Unified Parkinson's Disease Rating Scale

↑ = higher score is better; ↓ = lower score is better; * p <0.05; † p <0.008; ‡ p <0.007

The study by Singh et al. (Table 26) used stepwise discriminant function analysis to identify four factors (Hoehn and Yahr Stage 3, car test score, Hoehn and Yahr Stage 2 and other condition, and reaction time to brake) that correlated significantly with driving suitability (judged by a combination of clinical tests, examination, and on-road driving assessment) in individuals with PD. Factor Hoehn and Yahr Stage 2 was grouped with presence of other conditions to show significant correlation with driving suitability (the independent assessment of Hoehn and Yahr Stage 2 was found capable of "uncertainty" occurrence related to driving suitability when predicting driving ability in this study).(102) For all factors shown in Table 26, a normal correlation coefficient resulted from factoring all associated variables and related degree of association. The strongest degree of association and true predictability of driving suitability was found in Hoehn and Yahr Stage 3 (0.71) as shown below. Together, the four significant factors correctly classified 92% of the patients.

Table 26. Driving Ability Prediction Findings

Reference	Year	Factor	Driving Suitability	
			Coefficient (degree of association)	Significance of F
Singh et al.(102)	2007	H&Y Stage 3	0.7 (0.71)	p = 0
		Car test score	0.51 (0.68)	p = 0
		H&Y Stage 2 and other condition	0.32 (0.55)	p = 0.005
		Reaction time to brake	0.31 (0.45)	p = 0.008

H&Y = Hoehn and Yahr

Three studies by Uc et al. shared most of the same patients, but each evaluated different factors with a potential correlation with specific driving performance tasks during on-road testing. One study found significantly higher navigation impairment (as measured by at-fault safety errors, incorrect turns, and getting lost) among drivers with PD compared to neurologically normal controls. Multivariate analyses found that the most important predictors of at-fault safety errors among drivers with PD were visual processing speed and attention (Useful Field of View [UFOV]), while the most important predictors of incorrect turns were non-verbal memory (Complex Figure Test-Recall) and familiarity. No significant association was found with daily levodopa dosage or type of medication and driving performance outcomes.(103) Another study of the same patient group found that score on the Trail Making Test (TMT), which measures ability to switch attention between competing tasks, was the strongest multivariate predictor of at-fault safety errors during a landmark and traffic sign identification task.(105) The third study evaluated driving performance during simultaneous administration of the Paced Auditory Serial Addition Test (PASAT), which introduced controlled distraction to test multitasking ability while driving. Multivariate analysis identified TMT as the strongest predictor of at-fault safety errors during PASAT with baseline error status in the model.(104)

Table 27. Factors Significantly Correlated with Driving Performance Outcomes in Multivariate Analyses

Reference	Year	Assessment Variables	Driving Performance Data	
			Correlation coefficients	p-value
Uc et al.(103)	2007	**Visual processing speed and attention**	**At-fault safety errors**	
		UFOV	NR	NR, but p ≤0.05
		Non-verbal memory	**Incorrect turns**	
		CFT-RECALL	NR	NR, but p ≤0.05
		Familiarity	NR	NR, but p ≤0.05
Uc et al.(105)	2006	**Executive function**	**At fault safety errors (during landmark and traffic sign identification task)**	
		Trail-Making Test (B-A)	0.35	p <0.01
Uc et al.(104)	2006	**Executive function**	**At-fault safety errors (during Paced Auditory Serial Addition Test)**	
		Trail-Making Test (B-A)	NR	P ≤0.1

CFT = Complex Figure Test
UFOV = Useful Field of View
NR = Not reported

Heikkila et al. compared on-road driving performance of individuals with PD and neurologically normal age-matched controls. They found that drivers with PD committed significantly more risky faults and offences than the controls. Problems with driving in the PD group appeared mostly during urban driving rather than highway driving. Disease indices (H & Y scale, duration of disease, and MMSE scale) did not show significant correlation with driving test results. Stepwise regression found that three variables (slowness of visual processing, levodopa dosage, and age) explained 67% of the variation in faults and offences in the driving test for the PD group. When only laboratory variables were included, slowness of visual processing, slowness in recalling visual material, and errors in perception explained 62% of the variation in the PD group.(111)

Table 28 shows the results of a study comparing simulator crashes by Hoehn and Yahr Stage to healthy controls.(110) The data suggests an increased risk in simulator crash associated with increase in Hoehn and Yahr stage (p = 0.006). A heightened incidence of simulator crash among individuals with PD was found in Hoehn and Yahr Stages 2 (56%), 3 (90%) and 4 (100%) compared to healthy controls (20%), whereas Hoehn and Yahr Stage 1 (20%) was found comparable to healthy controls. However, these findings need to be replicated before reaching a definitive conclusion.

Table 28. Simulator Crash Rate Findings for Drivers with PD— Hoehn and Yahr Level Designated

Reference	Year	Simulator Crash Rate Data					
		Simulator Crashes per Person with PD H&Y Stage 1 % (n)	Simulator Crashes per Person with PD H&Y Stage 2 % (n)	Simulator Crashes per Person with PD H&Y Stage 3 % (n)	Simulator Crashes per Person with PD H&Y Stage 4 % (n)	Controls % (n)	Evidence of Increased Crash Risk? (p <0.01)
Zesiewicz et. al.(110)	2002	20 (10)	56 (16)	90 (10)	100 (3)	20 (25)	Yes (p = 0.006)

H&Y = Hoehn & Yahr Scale
PD = Parkinson's disease

Stolwyk et al. found significant correlations between certain neuropsychological testing measures and performance of drivers with PD on a driving simulator.(106) Performance measurement of Trail Making Test-subtest A (TMT-A) , Trail Making Test-subtest B (TMT-B), Symbol Digit Modalities Test (SDMT), Judgment of Line Orientation Test (JLO), Brixton Test, Weschler Adult Intelligence Scale-III of visual attention measurement (Pic. Completion), and Block Design correlated with driving performance measures. The strongest correlation was found between poor performance on the Brixton test (measuring ability in set formation/shifting) and driving performance measures (traffic signal [slow approach, deceleration and stopping point], slow mean curve speed, curve direction effect[lower adjustment], and lower variability of within curve lane position). In a companion study of the same patients, Stolwyk et al. found that older age and poor MMSE performance was significantly associated with lower traffic signal approach speed and lower mean curve speed on a driving simulator; older age was also significantly associated with later deceleration point. Drivers with PD who drove less often had an increased risk of driving through traffic signals, and were more reliant on internal cues to stop at traffic signals. Disease duration, UPDRS scores, and self-reported on-road crashes were not significantly associated with simulated driving performance.(107) For both studies, we cannot determine which of these variables would have remained significant had the authors conducted a multivariate analysis. Furthermore, neither of these studies evaluated the association of neuropsychological test measures with crashes on driving simulators.

Section Summary

The evidence is insufficient to determine with precision what risk factors or combination of risk factors truly defines when an individual with PD should stop driving. However, potential risk factors include movement restriction/decreased motor function, stage of PD, duration of PD, decreased cognitive function, and sudden onset of sleepiness (Strength of Evidence: Minimally Acceptable).

Direct Evidence – Crash Studies: Three studies in non-CMV driver populations provided direct evidence to address this question. One low-quality cohort study found that subgroups of patients with Hoehn and Yahr Stages 2 and 3 showed a significantly increased crash risk compared to control individuals without PD (p = 0.001, p = 0.008). No evidence of increased crash risk was found among patients in Hoehn and Yahr Stage 1. A low-quality cohort study evaluating outcomes in driving patterns among individuals with PD found that individuals with movement restriction had a significantly increased crash risk compared to

individuals without movement restriction (p = 0.034). One low-quality survey study evaluating outcomes of sudden onset of sleepiness and driving behavior found that disease severity, sleepiness, and driving exposure showed a significant association with crash prediction. However, these findings need to be replicated before a definitive conclusion can be reached. Limitations of the evidence supporting this conclusion are the small size of the evidence base (three studies) and overall low quality.

Indirect Evidence – Studies of Driving Tests and Driving Simulation: Twelve cohort studies (nine moderate-quality, three low-quality) evaluated outcomes indirectly associated with crash risk among non-CMV drivers with PD. One study showed a significant association of ESS scores and Inappropriate Sleep Composite Scores with risk of falling asleep while driving (p <0.001). Three studies' multivariate assessment of driving fitness showed a significant difference in factors (disease duration, contrast sensitivity, cognitive function, and motor function) associated with PD individuals who failed a driving assessment compared to individuals passing a driving assessment. However, predicting which individuals will pass or fail a driving assessment is not the same as predicting which individuals who pass a driving assessment will have an increased crash risk. Whether the variables identified in these studies can predict which patients with PD who pass a driving assessment are at increased risk of crash remains to be determined. Another study identified disease stage, car test score, and reaction time to brake as predictors of driving suitability using stepwise discriminant analysis.

Of the remaining studies, three studies that shared most of the same patients used multivariate analyses and identified various neuropsychological measures as predictors of at-fault safety errors and incorrect turns during on-road testing. No significant association was found with daily levodopa dosage or type of medication and driving performance outcomes. Another study used stepwise regression to determine that slowness of visual processing, levodopa dosage, and age explained 67% of the variation in faults and offenses in the on-road driving test for drivers with PD. Disease indices (H & Y scale, duration of disease,and MMSE scale) did not show significant correlation with driving results in this study.

The three remaining studies evaluated factors associated with simulated driving outcomes. One study found that a significant increase in simulator crash correlated with increasing Hoehn and Yahr stage (p = 0.006). The other two studies identified various neuropsychological measures as variables correlating with performance measures on a driving simulator. However, the possibility exists that some of these variables might not have remained significantly correlated with driving performance had a multivariate analysis been performed.

The findings of studies that used multivariate assessment or discriminant function analysis for predicting driving performance should be given greater consideration than the studies that did not as these studies attempt to isolate the true predictability of the associated risk factors evaluated within the studies. Also, studies that evaluated driving performance on the road should be given greater consideration than studies that evaluated driving performance on a simulator.

We were not able to assess the crash risk for PD among CMV drivers. The lack of studies enrolling CMV drivers with PD precludes one from determining whether CMV drivers with this condition are at an increased risk for a motor vehicle crash.

Key Question 2: What is the impact of pharmacotherapy for PD on driver safety?

Introduction

Options to treat PD can be categorized into nonpharmacological treatments, pharmacological treatments, and surgical approaches. While ideal therapy for PD would reverse symptoms or at least stop disease progression, no such treatment is available.(114) Therefore, current pharmacologic treatments focus on alleviating symptoms and improving quality of life. Classifications for pharmacotherapy include dopamine agonists, dopamine prodrugs, COMT inhibitors, MAO-B inhibitors, amantadine, and anticholinergics. Common side effects previously reported include nausea, dizziness, and somnolence (sleepiness). A listing of common side effects and treatment benefits of PD pharmacotherapy currently marketed in the U.S. is shown in Table 29 below.

Table 29. U.S. Pharmacotherapy for PD

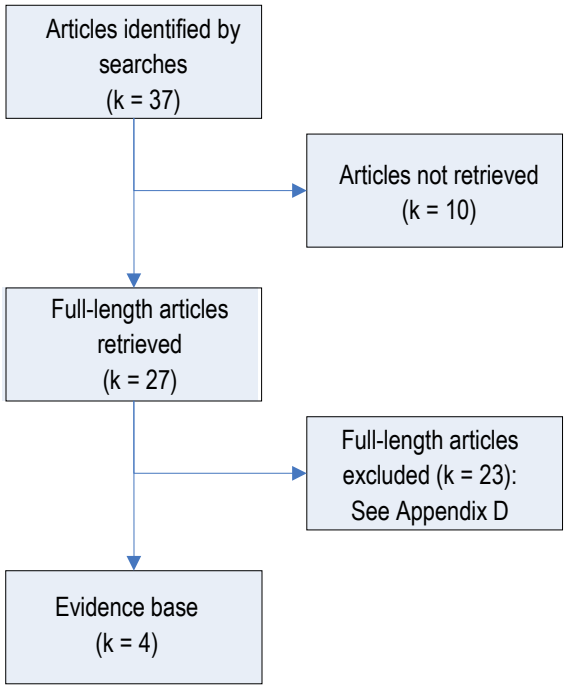
Category	Generic (Trade Name)	Common Side Effects	Intended Benefit
DOPAMINE AGONISTS			
Ergot Agonists	*bromocriptine* Parlodel®(115)	Sleep attacks, somnolence, nausea, hypotension, hallucinations, and confusion	May allow reduced dose of levodopa and in turn improvement of dyskinesia and "on-off" period
Non-Ergot Agonists	*pramipexole* Mirapex®(116)	Sleep attacks, somnolence, nausea, hypotension, and hallucinations	Effective in treating both early and advanced stages of PD; improvement in tremor
	ropinirole Requip®(117)	Sleep attacks, somnolence, hallucinations, hypotension, nausea, and headache	Effective in treating both early and advanced stages of PD; improvement in tremor
DOPAMINE PRODRUGS	*levodopa/carbidopa* Sinemet®(118)	Dyskinesias such as choreiform, dystonic, and other involuntary movements and nausea	Increases effectiveness of levodopa; improved mobility
	Sinemet CR®(119)	Dyskinesia, nausea, hallucinations, and confusion	Increases effectiveness of levodopa; improved mobility
	Parcopa®(120)	Somnolence, dizziness, headache, loss of appetite, nausea and vision change	Increases effectiveness of levodopa
COMT INHIBITORS	*tolcapone* Tasmar®(121)	Dyskinesia, nausea, sleep disorder, dystonia, and excessive dreaming	Increases effectiveness or "on" time of levodopa/carbidopa
	entacapone Comtan®(122)	Uncontrolled movements, nausea, diarrhea, and abdominal pain	Increases effectiveness or "on" time of levodopa/carbidopa
	levodopa, carbidopa, and entacapone Stalevo®(123)	Dyskinesia, nausea, diarrhea, and abdominal pain	Better control of symptoms on an extended daily period
MAO-B-INHIBITORS	*selegiline* Eldepryl®(124)	Agitation, insomnia, hallucinations, and nausea	As an adjunctive treatment for levodopa/carbidopa selegiline blocks the catabolism of dopamine
	selegiline HCL orally disintegrating tablet Zelapar®(125)	Dizziness, nausea, pain, headache, insomnia, rhinitis, dyskinesias, back pain, stomatitis, and dyspepsia	As an adjunctive treatment for levodopa/carbidopa selegiline blocks the catabolism of dopamine

Category	Generic (Trade Name)	Common Side Effects	Intended Benefit
	rasagiline Azilect®(126)	Dyskinesia, hypotension, headaches, joint pain, and indigestion	Initial monotherapy and adjunct to levodopa
AMANTIDINE	amantadine Symmetrel®(127)	Insomnia, dizziness, and nausea	Reduces fatigue, tremor ad bradykinesia in early stages and can reduce dyskinesias in advanced PD
ANTICHOLINERGICS	benztropine mesylate Cogentin®(128)	Weakness and inability to move muscle groups, mental confusion and excitement, dyskinesia	Reduces tremor and muscle rigidity

Identification of Evidence Base

The evidence base identification pathway for Key Question 2 is summarized in Figure 17. Our searches[3] identified a total of 37 articles that were potentially relevant to this key question. Following application of the retrieval criteria for this question (Appendix D), 27 full-length articles were retrieved and read in full. Four of these retrieved articles were found to meet the inclusion criteria (Appendix D) for this key question. Two of these studies shared the same patients (one was an extension study continued for longer follow-up), but each study has relevant data for different time periods. Table D-1 of Appendix D lists the 23 articles that were retrieved, read in full, and then excluded. The table also provides justification for their exclusion.

Figure 17. Development of Evidence Base for Key Question 2



[3] See Appendix A for search strategies.

Table 30. Evidence Base for Key Question 2

Reference	Year	Study Location	Country
Sleepiness			
Sethi et al.(129) Adler et al.(95)	1998, 1997	25 centers in several states	USA
Parkinson Study Group(130)	1997	20 centers in several states	USA
Shannon et al.(131)	1997	18 centers in several states	USA

Evidence Base

This subsection provides a brief description of the key attributes of the four studies that comprise the evidence base for Key Question 2. 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

No relevant crash studies were found for inclusion within the evidence base. Indirect evidence concerning one outcome potentially related to crash risk (sleepiness) characterized the studies provided within this section. Most of the included studies were randomized, controlled, double-blinded, parallel-group trials (RCTs)—a clinical trial methodology in which individuals are randomly assigned to a treatment or placebo group before determining the outcome of the pharmacotherapy studied. The randomized controlled trials (RCTs) were characterized by a cohort of individuals with PD randomly selected to receive dopamine agonist ropinirole or pramipexole or placebo over a time period to assess UPDRS and Hoehn and Yahr score change. One study was technically an extension study of one of the RCTs, where patients who completed the trial were given the option of continuing for an additional six months. Because many patients dropped out or elected not to continue, the study is technically a cohort study because the high dropout rates undermine the randomization process. However, double-blinding was maintained. Associated adverse events, including sleepiness, were also assessed for comparison between treatment and placebo groups. Studies were similar in how PD was defined and clinically confirmed (idiopathic, early years, Hoehn and Yahr Stages I-III, and UPDRS), and self-reporting of outcome. Specifically, these primary outcomes (UPDRS, Hoehn and Yahr motor score change, and sleep problems) were all self-reported using established testing instruments.

The primary characteristics of the four included studies that address Key Question 2 are presented in Table 31 below.

Table 31. Key Study Design Characteristics of Studies that Address Key Question 2

Reference	Year	Study Design	Comparison	How was PD Defined?	PD Clinically Confirmed?	Primary Outcome	Outcome Self-reported?
Sleepiness							
Sethi et al.(129)	1998,	Double-blinded cohort extension study (continuation of Adler et al.)	Treatment (Ropinirole) vs. placebo Approximately half of the patients in each group were taking concomitant selegiline. Carbidopa/levodopa was added for symptom control in selected patients	H&Y Stage	Yes. Clinician assessment	Percent of patients receiving monotherapy	Yes
Adler et al.(95)	1997	Double-blinded, parallel-group RCT				UPDRS motor examination	
Parkinson Study Group(130)	1997	Double-blinded, parallel-group RCT	Treatment (Pramipexole) arms vs. Placebo	Early Idiopathic PD <7 years in H&Y Stages I-II	Yes. UPDRS & H&Y stage assessment	UPDRS, H&Y score change	Yes
Shannon et al.(131)	1997	Double-blinded, parallel-group RCT	Treatment (Pramipexole) vs. Placebo	Idiopathic PD individuals in H&Y Stages I-III	Yes. UPDRS & H&Y stage assessment	UPDRS II (ADL) and III (motor) score change	Yes

ADL = Activities of Daily Living
H&Y = Hoehn and Yahr
N/A = Not Applicable
NR = Not Reported
PD = Parkinson's disease
RCT = Randomized controlled trial
UPDRS = Universal Parkinson's Disease Rating Scale

Quality of Evidence Base

Our analysis found that the quality ratings for the four included studies varied from moderate to high (median quality: moderate). For these studies we used the ECRI Institute Quality Scale I: Controlled Trials (the instrument is shown in detail in Appendix F). The quality of RCTs is less limited than other study designs due to random assignment that controls for known and unknown confounding factors; thus, the quality rating of these studies are typically moderate to high. The controlled trials rated as moderate reported a higher participant attrition rate and one did not provide detailed blinding information.

Our quality assessments of the studies in the evidence base for Key Question 2 are summarized in Table 32 below. Complete details of our quality assessment can be found in the study summary tables presented in Appendix G.

Table 32. Quality of the Studies That Assess Key Question 2

Reference	Year	Quality Scale Used	Quality
Sleepiness			
Sethi et al.(129) Adler et al.(95)	1998, 1997	ECRI Institute Quality Scale I: Controlled Trials	Moderate
Parkinson Study Group(130)	1997	ECRI Institute Quality Scale I: Controlled Trials	High
Shannon et al.(131)	1997	ECRI Institute Quality Scale I: Controlled Trials	Moderate

Generalizability of Evidence to Target Population

The purpose of this subsection is to provide details of the extent to which individuals enrolled in the studies that address Key Question 2 are similar to CMV drivers in the United States. The generalizability of the findings of all included studies to CMV drivers is unclear as none of the included studies examined PD pharmacotherapy impact among CMV drivers. Another factor that may limit the generalizability of the findings included in this section of the evidence report is the lack of studies investigating drug classes other than dopamine agonists used for PD pharmacotherapy. Consequently, the ability to only assess one type of drug treatment lowers the possibility of generalizing these findings. In addition, the mean age of patients in these studies was somewhat older (60 to 63) than the CMV driving population, and women were overrepresented relative to the CMV driver population. Finally, CMV drivers may be under more pressure to drive even when experiencing symptoms related to pharmacotherapy for PD.

Important characteristics of the individuals included in the studies that address Key Question 2 are presented in Table 33 shown below.

Table 33. Generalizability of Studies that Address Key Question 2

Reference	Year	Number of Individuals with-PD Included (n =)	PD Duration (mean)	Pharmacotherapy Duration (PD)	Pharmacotherapy Type	% Drivers with PD	Mean Age Distribution (SD) *	% Male (n)	% CMV Drivers	Generalizability to Target Population?
Sleepiness										
Sethi et al.(129)	1998	147	23.5 months (Ropinirole group) 22.6 months (Placebo group)	6 months	Ropinirole Approximately half of the patients in each group were taking concomitant selegiline. Carbidopa/levodopa was added for symptom control in selected patients	NR	61.6±11.1(Ropinirole) 62.1 ±10.8(Placebo)	63(92)*	0	Unclear
Adler et al.(95)	1997	241		12 months						
Parkinson Study Group(130)	1997	264	<7years	10 weeks	Pramipexole	NR	**Placebo** (n = 51): 60.4 (12.0)	**Placebo:** 62.7% (n = 51)	0	Unclear
							1.5 mg/d (n = 54): 60.3 (10.5)	**1.5 mg/d:** 64.8% (n = 54)		
							3.0 mg/d (n = 50): 62.2 (11.1)	**3.0 mg/d:** 62.0% (n = 50)		
							4.5 mg/d (n = 54): 62.8 (10.5)	**4.5 mg/d:** 63.0% (n = 54)		
							6.0 mg/d (n = 55): 62.8 (11.4)	**6.0 mg/d:** 69.1% (n = 55)		
Shannon et al.(131)	1997	335	1.8 years	31 weeks	Pramipexole	NR	62.7	61%*	0	Unclear

NR = Not Reported
PD = Parkinson's disease

*Calculated by ECRI Institute from reported data.

Findings

Impact of Pharmacotherapy for PD on Driver Safety

Of the studies that met the inclusion criteria for Key Question 2, none presented data that is directly relevant to CMV drivers and the impact of pharmacotherapy for PD on driver safety. The included studies evaluated the effect of various dopamine agonists on one indirect outcome (sleepiness), which may be associated with driver safety.

One double-blinded RCT (Adler et al.) reported the number of patients who experienced somnolence within six months after receiving either ropinirole or placebo.(95) Patients who completed this trial were given the option of entering a continuation study (Sethi et al.) for an additional six months (with double-blinding maintained).(129) Results of this RCT and its subsequent continuation study appear in Table 34. Only about 60% of patients enrolled in the initial six-month study opted to enter the continuation study. The initial six-month study found a statistically significant seven-fold increase in the risk of somnolence associated with ropinirole use compared to placebo. The effect size in the continuation study was smaller and not quite statistically significant, which may have been due to the smaller patient population and smaller overall number of events.

As shown in Table 35, both RCTs that evaluated pramipexole had statistically similar results (Parkinson Study Group(130) closely misses the cut-off value to determine statistical significance). Thus, a summary estimate of the relative risk (risk ratio) of somnolence was calculated for these two RCTs. The meta-analysis showed a statistically significant summary relative risk (p = 0.002), indicating an elevated risk of sleepiness among individuals taking pramipexole. The results of the meta-analysis appear in Figure 18.

Table 34. Pharmacotherapy (Ropinirole) Impact on Somnolence Adverse Event Findings

Reference	Year	Somnolence Adverse Event Rate Data			
		Ropinirole Treatment Group (n affected)	Placebo Group (n affected)	Relative Risk (95% CI)*	Evidence of Decreased Driver Safety? (p <0.05)*
Adler et al.(95)	1997	42/116	6/125	7.54 (3.33-17.08)	Yes. p <0.0001
Sethi et al.(129)	1998	9/70	3/77	3.30 (0.93-11.70)	No. p = 0.065

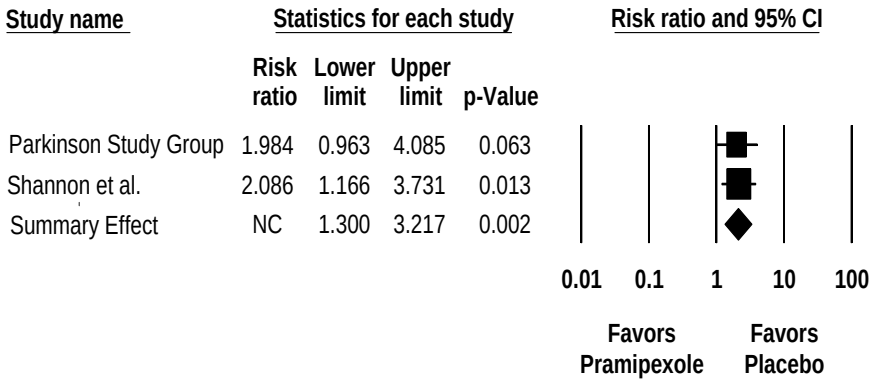
* Calculated by ECRI Institute from reported data.

Table 35. Pharmacotherapy (Pramipexole) Impact on Somnolence Adverse Event Findings

Reference	Year	Somnolence Adverse Event Rate Data			
		Pramipexole Treatment Group (n affected)	Placebo Group (n affected)	Relative Risk (95% CI)*	Evidence of Decreased Driver Safety? (p <0.05)*
Parkinson Study(130)	1997	58/213	7/51	1.984 (0.963-4.085)	No. p = 0.063
Shannon et al.(131)	1997	30/163	15/170	2.086 (1.166-3.731)	Yes. p = 0.013

CI = Confidence Interval

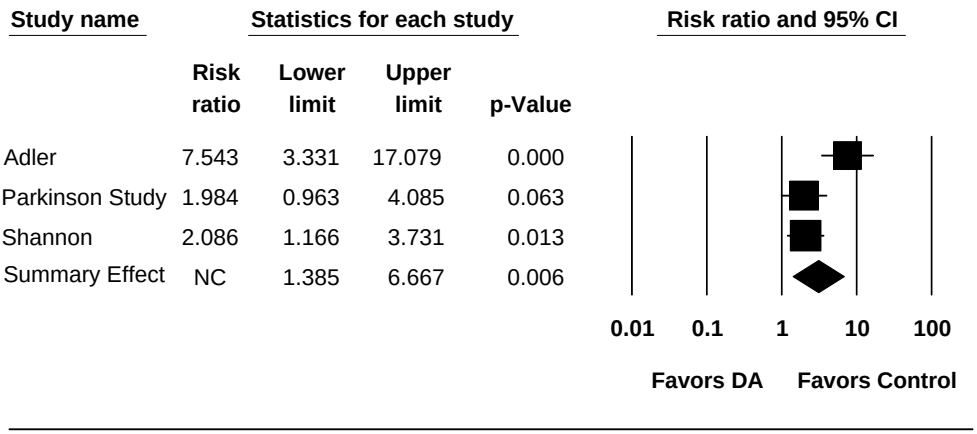
Figure 18. Results of Random Effects Meta-Analysis—Risk of Somnolence in Individuals Undergoing Pharmacotherapy with Pramipexole for PD



NC = Not Calculated

We also conducted a random effects meta-analysis of all three RCTs since all evaluated dopamine agonists (Figure 19). Adding the ropinirole study by Adler et al. introduced substantial heterogeneity into the findings (I^2 = 73%). Without additional studies that evaluated ropinirole, we cannot determine whether ropinirole leads to a greater risk of somnolence than pramipexole or whether the larger risk ratio was due to other factors. However, the evidence suggests that as a group, dopamine agonists may lead to an increased risk of somnolence in patients with PD. Since the median study quality is moderate and the evidence was robust (see Appendix H for sensitivity analysis), the strength of evidence is moderate.

Figure 19. Results of Random Effects Meta-Analysis—Risk of Somnolence in Individuals Undergoing Pharmacotherapy with Dopamine Agonists for PD



DA = Dopamine Agonists
NC = Not Calculated

Section Summary

Evidence suggests that use of dopamine agonists may lead to somnolence (sleepiness) in individuals with PD. (Strength of Evidence: Moderate) The evidence is insufficient to determine whether other types of pharmacotherapy may affect driver safety. Whether measures of somnolence among individuals with PD taking pharmacotherapy can predict actual crash risk cannot be determined from currently available evidence.

Direct Evidence: No included studies provided direct evidence of crash risk with noncommercial drivers.

Indirect Evidence: The four included studies (ranging from moderate to high quality) evaluated the effect of dopamine agonists on an indirect outcome (sleepiness), which may be associated with driver safety. The results of a meta-analysis of two RCTs found that individuals with PD given pramipexole tend to be at an increased risk of somnolence compared to those given placebo (RR 95% CI: 1.31-3.29, p = 0.002). Another RCT found a large and significant increase in risk of somnolence among patients using ropinirole compared to patients given placebo (p <0.0001).The results of a meta-analysis combining the three RCTs showed a statistically significant and robust risk of somnolence among patients with PD treated with dopamine agonists (p = 0.006).

We were not able to assess the impact of pharmacotherapy for PD on driver safety among CMV drivers. The paucity of data from studies enrolling CMV drivers treated with PD pharmacotherapy precludes one from determining whether CMV drivers with this type of condition are at an increased risk for a motor vehicle crash.

Key Question 3: Are individuals with Multiple Sclerosis (MS) at an increased risk of a motor vehicle crash? If so, what factors associated with MS are predictive of an increased crash risk?

Introduction

MS is a chronic progressive neurological disorder resulting in the inflammation and damage to myelin (protective nerve coating) and other cells within the central nervous system.(132) MS can affect any area of the brain, optic nerve, or spinal cord and can cause almost any neurological symptom.(133) Related disease complications may include:

- Cognitive dysfunction
- Spasticity (increased stiffness)
- Visual loss or pain
- Loss of sensation
- Fatigue
- Loss of bladder or bowel control

Incidence of MS in the United States has been estimated at 4.2 cases per 100,000 with prevalence rates ranging from 266,000 to 400,000.(134,135) Average age of onset is typically between the ages of 20 and 50 years, with MS approximately two to three times more common in women than men.(135) MS is the most frequent cause of neurological disability in early to middle adulthood.(136)

MS can affect the central nervous system in an unpredictable manner. The disorder may frequently manifest into varying degrees of paresis and spasticity, visual blurring, sensory disturbances, diplopia, ataxia, fatigue, vertigo, paroxysmal attacks, and cognitive dysfunction—any of which may impair driving.(136) Cognitive impairment alone occurs in about half of all individuals diagnosed with MS and has been shown to affect attention and visual perceptual skills, information processing speed, and executive function.(137,138)

Stages of Disease

Based on the course of disease progression, individuals may be diagnosed as having one of four distinct forms of MS: relapsing remitting, secondary progressive, primary progressive, and progressive relapsing. Clinical phases of the disease may vary depending upon level of flare-up, absence or presence of remission, and functional deterioration as shown in Table 36 below.

Table 36. MS Disease Phases(139)

Forms of Multiple Sclerosis	Symptoms	Frequency (%)
Relapsing Remitting (RRMS)	• clearly defined flare-ups • episodes of heightened deterioration of neurologic function • periods of partial/complete remission	85%
Secondary Progressive (SPMS)	• initially develop RRMS • disease steadily worsens • occasional flare-ups and remissions	50% of patients with RRMS develop SPMS within 10 years of diagnosis
Primary Progressive (PPMS)	• slow steady deterioration in function from disease onset • no distinctive relapses or remissions	10%
Progressive Relapsing (PRMS)	• slow steady deterioration in function from disease onset • clearly defined acute flare-ups with/without remission	5%

Treatments

Management of MS may be handled by drug therapy such as "disease modifying" and symptomatic therapies, and non-drug therapy such as physical therapy and cognitive rehabilitation. The objective of drug therapies is threefold; reduce the frequency and severity of clinical attacks (relapses); reduce the accumulation of lesions with the brain and spinal cord; and slow down the accumulation of disabilities.(139) Several disease-modifying agents such as beta interferons, glatiramer acetate and mitoxantrone have been approved for use in early stages of the disease (RRMS). Only one agent is approved for use in later disease stages (SPMS and PRMS) while there is currently no FDA-approved treatment for primary progressive muscular sclerosis (PPMS).

Identification of Evidence Base

The evidence base identification pathway for Key Question 3 is summarized in Figure 20. Our searches[4] identified a total of seven articles that were potentially relevant to this key question. Following application of the retrieval criteria for this question (Appendix D), six full-length articles were retrieved and read in full. Four of these retrieved articles were found to meet the inclusion criteria (Appendix D) for this key question. Table D-3 of Appendix D lists the two articles that were retrieved, read in full, and then excluded. The table also provides justification for their exclusion.

Figure 20. Development of Evidence Base for Key Question 3

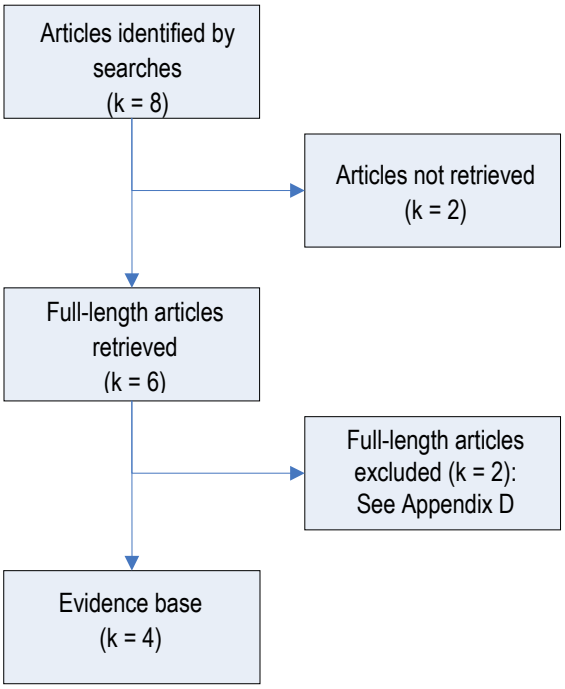


Table 37. Evidence Base for Key Question 3

Reference	Year	Study Location	Country
Crash			
Lings(136)	2002	Odense	Denmark
Schultheis et al.(140)	2002	New Jersey	USA
Road Test			
Lincoln and Radford(141)	2008	Nottingham	UK
Driving Simulator			
Schultheis et al.(137)	2001	New Jersey	USA

[4] See Appendix A for search strategies.

Evidence Base

This subsection provides a brief description of the key attributes of the four studies that compose the evidence base for Key Question 3. 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

Two relevant crash studies and two driving performance studies (one road test and one driving simulator study) met the inclusion criteria for this question. These studies used a similar study design (cohort), comparison (individuals with MS versus no MS [healthy controls]), and criteria for clinical confirmation. The two studies by Schultheis et al. enrolled the same individual patients; because each study reported different outcomes (crash and simulated driving), we evaluate the findings separately. The primary characteristics of the included studies that address Key Question 3 are presented in Table 38. Schultheis et al. specifically included patients with MS who had minimal or no physical involvement of their disease, because they wanted to eliminate the confounding effect of physical limitation in their assessment of cognitive factors that might influence driving. In contrast, the study by Lincoln and Radford included patients with a spectrum of physical limitations, ranging from independent mobility to reliance on a wheelchair. The majority of patients in the study had difficulty walking.-Lings et al. did not provide enough information to estimate the severity of MS symptoms in their study population. However, the mean duration of MS was 14.1 years (range 0.1-44.5 years) for the patients in this study; a longer duration of MS increases the likelihood that some of these patients had physical limitations.

Table 38. Key Study Design Characteristics of Studies That Address Key Question 3

Reference	Year	Study Design	Comparison	How was MS Defined?	MS Clinically Confirmed?	Severity of MS	Factors Controlled for (if compared to non MS)?	Driving Exposure Controlled for?	Primary Outcome	Definition of Crash	Outcome Self-reported?
Crash Studies											
Lings(136)	2002	Retrospective Cohort	MS vs. No MS	Diagnosis of MS 340 (ICD 8th revision)	Yes. Hospital registry (emergency room visits)	NR	Age, gender, residence, exposure period*	Yes. (Only years of licensure not miles driven)	Crash-related medical treatment	Collision with other cars recorded in the AAG	No
Schultheis et al.(140)†	2002	Cohort†	MS vs. No MS	Relapsing-remitting (59%), secondary progressive (7%), primary progressive (4%), or undefined course (30%)	Yes. Medical records	Minimal or no physical limitation	Age, gender, and driving experience	Yes. (Only years of driving not miles driven)	Crash	State reported DMV records reported crash in previous 5 years	No
Road Test Studies											
Lincoln and Radford(141)	2008	Cohort†	Fail MS Drivers vs. Pass MS Drivers (Road Test)	Clinic assessment	Yes. Clinic referral patients	Difficulty walking (38%), assistance with mobility required (24%), wheelchair bound (15%), independently mobile (24%)	N/A	NR	Driving performance (road test)	NR	No
Driving Simulator Studies											
Schultheis et al.(137)†	2001	Cohort†	MS+, MS- vs. No MS	Relapsing-remitting (61%), secondary progressive (7%), primary progressive (4%), or undefined course (29%)	Yes. Medical records	Minimal or no physical limitation	Age, gender and driving experience	Yes	Driving performance (simulated)	N/A	Yes

AAG = Accident Analysis Groups' Register (study hospital only)
DMV = Department of Motor Vehicles
ICD = International Classification of Diseases
MS = Multiple Sclerosis
MS+= Multiple Sclerosis with cognitive impairment
MS- = Multiple Sclerosis without cognitive impairment
N/A = Not Applicable

* Exposure period is defined as the period of time individuals held a driver's license.

† A cohort study in which individuals are followed over a time period to determine development of the outcome.

Quality of Evidence Base

Our analysis using the Newcastle Ottawa Scale for Cohort Studies(142) found that the quality of all included studies was moderate. The quality rating of cohort studies can never be high for reasons outlined in earlier sections. However, the crash studies improved their quality scores by using outcome data from a crash registry and state driving records rather than self-reported data. Further, the cohorts within each study were relatively comparable. One crash study and the simulator driving study (which enrolled the same individual patients) used outcome data from a selected group of individuals within the MS community that may not be truly representative of the average MS individual in the community. The quality assessment instruments are shown in Table G-3, Appendix G. Quality assessment findings for the included studies composing the evidence base for Key Question 3 are summarized in Table 39. Complete details of our quality assessment can be found in the study summary tables presented in Appendix G.

Table 39. Quality of the Studies That Assess Key Question 3

Reference	Year	Quality Scale Used	Quality
Crash Studies			
Lings(136)	2002	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Schultheis et al.(140)	2002	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Road Test Studies			
Lincoln and Radford(141)	2008	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate
Driving Simulator Studies			
Schultheis et al.(137)	2001	Revised Newcastle-Ottawa Quality Assessment Scale for Cohort Studies	Moderate

Generalizability of Evidence to Target Population

The purpose of this subsection is to provide details of the extent to which individuals enrolled in the studies that address Key Question 3 are similar to CMV drivers in the United States. None of the included participants in the studies were CMV drivers. Further, women are overrepresented in the evidence-based study population compared to a CMV driver population (the proportion of men was reported as 37.5% and 50%). Due to these factors, the generalizability of the population in the evidence base to CMV drivers is unclear. Important characteristics of the individuals included in the studies that address Key Question 3 are shown in

Table 40 below.

Table 40. Generalizability of Studies That Address Key Question 3

Reference	Year	Number of Individuals with-MS Included (n)	Diagnosis (MS)	Mean Duration of MS (SE)*	% Drivers with MS	Age Distribution (SD) **	% Male	% CMV Drivers	Driving Exposure (i.e., average miles driven annually)	Driving Conditions (e.g., night driving, driving alone)	Generalizability to Target Population?
Crash Studies											
Lings(136)	2002	197	Yes, hospital register	14.1 (range 0.1-44.5)	26.5%	Female (NR-range of 21.6-82.8); Male (22.3-81.4)	49.7	0	NR	Road traffic	Unclear
Schultheis et al.(140) †	2002	27	Yes, medical records	MS+8.9(±1.8); MS(-)10.3(±2.3)	61.4%**	MS+45.5(±2.3); MS(-)40.9(±2.6)	37.5% **Total (MS+ -: 46%; MS(-): 29%)	0	Yes; years and days/week driving	Community-dwelling	Unclear
Road Test Studies											
Lincoln and Radford(141)	2008	34	Yes, clinician assessment	9.3(9.82)	100%	45.9(10.4)	50	0	Yes; 23.8 mean years driving (SD, 9.07)	Public road	Unclear
Driving Simulator Studies											
Schultheis et al.(137)	2001	28	Yes, medical records	MS+8.9(±1.8); MS(-)10.4(±2.2)	62.2%**	MS+40.9(±2.6); MS(-)45.6(±2.1)	MS+ -: 46%; MS(-): 33%	0	Yes; years and days/week driving	Simulated on-road test assessment	Unclear

MS = Multiple Sclerosis
MS+ = MS individuals with cognitive impairment
MS- = MS individuals without cognitive impairment
NR = Not Reported

* Standard Error was reported instead of Standard Deviation (SD)
** Calculated by ECRI Institute from reported data.

Findings

Impact of MS on Crash Risk

Two included studies provided direct evidence (crash data) measuring the impact of MS on crash risk among non-CMV drivers with MS. However, we were able to calculate odds ratios for both studies and combine the data in a random-effects meta-analysis. As shown in Figure 19, the 95% confidence interval around the summary odds ratio is statistically significant. Although this finding is not robust with only two studies, it suggests that at least some patients with MS have an elevated risk of crash compared to drivers without MS.

Table 41 shows the study results comparing crash risk of individuals with MS and healthy controls. Although the summary effect size in both studies suggested increased crash risk among drivers with MS, the findings did not reach statistical significance in either study. However, we were able to calculate odds ratios for both studies and combine the data in a random-effects meta-analysis. As shown in Figure 19, the 95% confidence interval around the summary odds ratio is statistically significant. Although this finding is not robust with only two studies, it suggests that at least some patients with MS have an elevated risk of crash compared to drivers without MS.

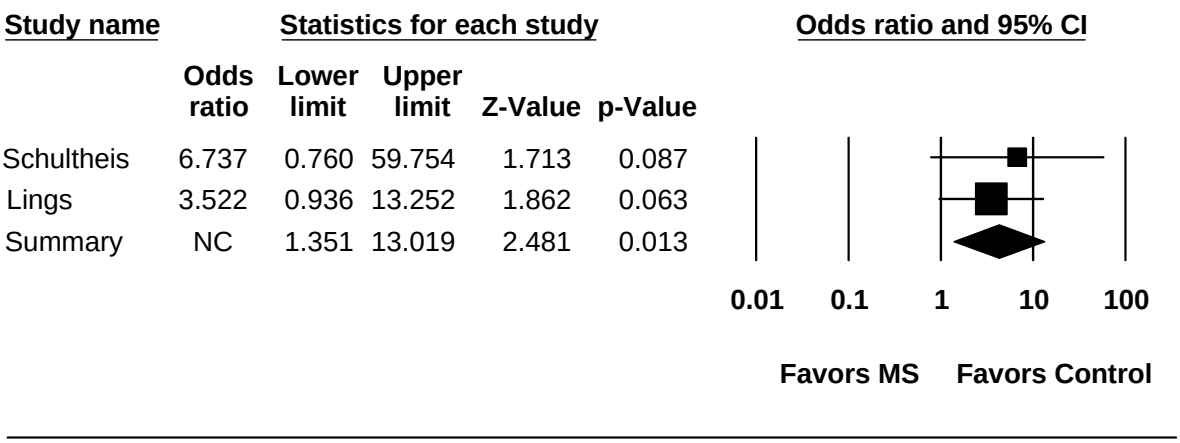
Table 41. Crash Risk Findings for MS versus No MS Individuals

Reference	Year	Crash		No Crash		OR** (95% CI)	Evidence of Increased Crash Risk? (p <0.05)**
		No MS (n)	MS (n)	No MS (n)	MS (n)		
Schultheis et al.(140)	2002	1	All MS: 8	16	All MS:19	6.737 (0.760-59.754)	No. p = 0.087
Reference	**Year**	**Crash Rate Data**					
		MS Crashes/ Person-Years	MS Crash Rate*	Control (No MS) Crashes/ Person-Years	Control (No MS) Crash Rate*	Rate Ratio (95% CI)	Evidence of Increased Crash Risk? (p <0.05)
Lings(136)	2002	5/1500.44 person-years	3.3	4/4084.30 person-years	0.98	3.4 (0.73-17.15)	No. (p = 0.129)**

CI = Confidence Interval
MS = Multiple Sclerosis
MS+ = MS individuals with cognitive impairment
MS- = MS individuals without cognitive impairment
OR = Odds ratio

* per 1,000 person-years
** Calculated by ECRI Institute from reported data.

Figure 21. Results of Random Effects Meta-Analysis—Odds of Crash among Drivers with MS versus Healthy Drivers



NC – not calculated

Impact of Cognitive Impairment on Increased Crash Risk

Three studies(137,140,141) provided direct evidence (crash data) or indirect evidence (driving performance) that addressed this question. The findings of the evidence base are shown in **Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**, and **Error! Reference source not found.**.

Direct Evidence (Crash Data)

One study(140) provided direct evidence that cognitive impairment may affect crash risk among non-CMV drivers with MS. As shown in **Error! Reference source not found.**, the sub-group of MS patients with cognitive impairment in the study showed elevated odds of crash compared to control individuals without MS, whereas the subgroup of MS patients without cognitive impairment did not show elevated odds of crash compared to controls. This finding suggests that cognitive impairment caused by MS may be a more important predictor of crash risk than simply having MS. However, this finding needs to be replicated before a definitive conclusion can be reached.

Table 42. Crash Risk Findings for MS versus No MS Individuals

Reference	Year	Crash		No Crash		OR* (95% CI)	Evidence of Increased Crash Risk? (p <0.05)*
		No MS (n)	MS (n)	No MS (n)	MS (n)		
MS and Cognitive Impairment							
Schultheis et al.(140)	2002	1	MS-: 1	16	MS-: 13	1.231 (0.070-21.638)	No. p = 0.887
			MS+: 7		MS+: 6	18.667 (1.879-185.399)	Yes. p = 0.012

CI = Confidence Interval
MS = Multiple Sclerosis
MS+ = MS individuals with cognitive impairment

MS- = MS individuals without cognitive impairment
OR = Odds ratio
* Calculated by ECRI Institute from reported data.

Indirect Evidence (Road Test and Simulated Driving Performance)

Cognitive Impairment

Two studies provided indirect evidence that cognitive impairment may affect driving performance of non-CMV drivers with MS. Lincoln and Radford evaluated the association between cognitive performance and road test outcome (pass/fail).(141) As shown in **Error! Reference source not found.**, individuals who passed the road test received significantly better scores on six cognitive test scores when compared to those who failed ($p < 0.05$). These included two tests from the Stroke Drivers Screening Assessment (SDSA - Dot Cancellation false positives and Road Sign Recognition) and four tests from the Adult Memory and Information Processing Battery (AMIPB - Figure Recall Copy, Design Learning Interference, IP A Adjusted Score, and IP B Adjusted Score). No significant between-group difference was found among other cognitive tests, including the Paced Auditory Serial Addition Test (PASAT), the Stroop test, and the Test of Motor Impersistence (data not shown). Discriminant function analysis identified SDSA Dot Cancellation (time, errors, and false positives), SDSA Road Sign Recognition, Design Learning total, and AMIPB IP Task B adjusted score as variables predicting pass or fail on the driving assessment for both patients with PD and controls. Two other variables significant in univariate comparisons (AMIPB Figure Recall Copy and IP Task A) were excluded from the model due to a ceiling effect and redundancy with IP Task B, respectively. The resulting equations correctly classified the driving test outcome for 85% of those who failed the road test and 90% of those who passed the road test.

Table 43. Comparison of MS Drivers (Pass) versus MS (Failed) Road Test in Cognitive Test Scores

Reference	Year	Cognitive Test	Driving Test Performance		
			Pass MS Driver (n = 21)	Fail MS Driver (n = 13)	Findings Significant? (p <0.05)[a]
Lincoln and Radford(141)	2008	**SDSA Dot Cancellation Time**			
		Median (Interquartile range)	488 (375-694)	560 (442-687)	No. p = 0.16
		SDSA Dot Cancellation Errors			
		Median (Interquartile range)	8 (2-17)	10 (3-23)	No. p = 0.21
		SDSA Dot Cancellation False Positives			
		Median (Interquartile range)	0 (0-0)	1 (0-5)	Yes. p = 0.004
		SDSA Road Sign Recognition			
		Median (Interquartile range)	9 (5-12)	6 (2-7)	Yes. p = 0.005
		AMIPB Figure Recall Copy			
		Median (Interquartile range)	76 (75-76)	75 (69-76)	Yes. p = 0.04
		AMIPB Design Learning Interference			
		Median (Interquartile range)	4 (3-7)	3 (1.5-5)	Yes. p = 0.03
		AMIPB IP A Adjusted Score			

Reference	Year	Cognitive Test	Driving Test Performance		
			Pass MS Driver (n = 21)	Fail MS Driver (n = 13)	Findings Significant? (p <0.05)[a]
		Median (Interquartile range)	60.3 (40-76)	37.2[b] (24-55)	Yes. p = 0.02
		AMIPB IP B Adjusted Score			
		Median (Interquartile range)	58.9 (38-74)	39.4[b] (34-53)	Yes. p = 0.04

AMIPB = Adult Memory and Information Processing
SDSA = Stroke Drivers Screening Assessment

[a] Comparison using Mann-Whitney U-test.
[b] AMIPB IP n = 12 in Fail group.

The remaining study by Schultheis et al.(137) compared estimated crash risk involvement of individuals with MS to healthy controls based on the UFOV test performance (**Error! Reference source not found.**). All but one of the patients were included in the crash study by Schultheis et al.(140) The data suggests an elevated risk among MS individuals with cognitive impairment within one of three risk categories (very low to low) when compared to healthy controls ($p < 0.01$). The subgroup of MS patients without cognitive impairment did not show a significant difference in estimated crash risk in any risk category. Further, all healthy controls assessed had an overall UFOV of very low to low estimated risk (100%) compared to lower incidence among MS individuals without cognitive impairment (86%) and MS individuals with cognitive impairment (64%). The study also found a heightened incidence of estimated crash risk among cognitively impaired individuals with MS in the moderate (7%) and high (29%) crash risk categories compared to healthy controls (0% for both), though no significant difference was concluded from the subcategory analysis. Slightly similar results were found in the MS subgroup of individuals without cognitive impairment as heightened incidence occurred in the moderate crash risk subcategory (14%).

Error! Reference source not found. shows results from the same study comparing estimated crash risk involvement of individuals with MS to healthy controls based on Neurocognitive Driving Test (NDT) performance. The study reported longer time responses among MS individuals with cognitive impairment (MS+) when compared to MS individuals without cognitive impairment (MS-), an indication of slower performance in the MS+ group. These findings indicate a significant difference in performance between the two MS groups ($p < 0.0001$). However, there was no significant difference found among MS groups in total error scores from task performance ($p = 0.678$) as error score results were comparable.

The findings of these studies suggest that cognitive impairment caused by MS may be a predictor of unsafe driving, but this is based only on indirect outcomes that may or may not be associated with actual crash risk. These findings should be replicated in other studies before any conclusions can be reached.

Table 44. UFOV Performance Among MS versus No MS Individuals

Reference	Year	UFOV Driving Test Performance				
		MS (n)	Estimated Risk Category (% individuals in each category)	No MS (n)	Estimated Risk Category (% individuals in each category)	Findings Significant? (p <0.01)
MS and Cognitive Impairment						
Schultheis et al.(137)	2001	With CI (13)	Very Low to Low (64%)	17	Very Low to Low (100%)	Yes
			Moderate (7%)		Moderate (0%)	No
			High (29%)		High (0%)	No
		Without CI (15)	Low (86%)		Low (100%)	No
			Moderate (14%)		Moderate (0%)	No
			High (0%)		High (0%)	No

CI = Cognitive Impairment
UFOV = Useful Field of View

Table 45. Driving Performance Findings among MS Individuals with Cognitive Impairment versus MS Individuals without Cognitive Impairment

Reference	Year	Task Type	Neurocognitive Driving Test Performance		
			MS+ (n = 13)	MS- (n = 15)	Findings Significant? (p <0.05)
Schultheis et al.(137)	2001	**Timed Responses (msec)**			
		NDT-LAT Score (SEM)	4416 (313)	2695 (155)	Yes. p <0.0001
		Errors			
		NDT-ERR Score (SEM)	3.4 (0.76)	3.1 (0.44)	No. p = 0.678

MS+ = MS individuals with cognitive impairment
MS- = MS individuals without cognitive impairment
NDT-ERR = total error score averaged from simple reaction time, choice reaction time, driving scenarios, and visual field task
NDT-LAT = total latency time score on pre-driving questions, simple reaction time, choice reaction time, initiation time , and visual task latency time
SEM = Standard Error mean

Section Summary

Currently available evidence suggests that some drivers with MS may have an elevated risk of crash compared to drivers without MS. (Strength of Evidence: Minimally Acceptable) Preliminary evidence suggests that crash risk may be increased predominantly among a subgroup of individuals with MS and cognitive impairment, while individuals with MS but no cognitive impairment may not have an increased crash risk. However, more evidence is needed for a definitive conclusion concerning the effect of other factors on crash risk among drivers with MS.

Direct Evidence: Two moderate-quality cohort studies evaluated outcomes directly associated with crash risk among non-CMV drivers with MS. Although the summary effect size in both studies suggested increased crash risk among drivers with MS, the findings did not reach statistical significance in either study. However, a pooled analysis of data from both studies found statistically significant elevated odds of crash among drivers with MS compared to drivers without MS.

In one of these studies a subgroup of MS patients with cognitive impairment showed significantly increased crash risk compared to control individuals without MS, whereas a subgroup of MS patients without cognitive impairment did not show significantly increased crash risk compared to controls. The individuals in this study had minimal or no physical limitations, so they were not in a severe stage of MS. This finding suggests that cognitive impairment caused by MS may be a more important predictor of crash risk than simply having MS. However, this finding needs to be replicated before a definitive conclusion can be reached concerning the effect of other factors on crash risk among drivers with MS.

Indirect Evidence – Road Test and Driving Simulator Studies: *Two moderate quality cohort studies evaluated outcomes that may be indirectly associated with crash risk among non-CMV drivers with MS. One study found that MS drivers who failed a road test scored significantly worse ($p < 0.05$) on six out of 23 cognitive tests compared to MS drivers who passed a road test. This study included patients with a wide spectrum of disease severity, ranging from independent mobility to wheelchair dependence. In the other study, assessment of UFOV performance related to simulated driving showed that a subgroup of MS patients with cognitive impairment had a significant increase in estimated crash risk ($p < 0.01$) compared to control individuals without MS, whereas a subgroup of MS patients without cognitive impairment did not show a significant increase in estimated crash risk compared to the control group. Assessment of neurocognitive driving performance within the same study showed a significant increase in latency time scores for MS patients with cognitive impairment compared to MS patients without cognitive impairment and healthy controls. The errors subcategory did not show a significant difference among these three groups. The patients in this study had minimal or no physical limitations. Whether these findings have any relationship with actual crash risk remains uncertain. Limitations of this evidence include small sample size (two studies) and moderate study quality.*

We were not able to assess the crash risk for MS among CMV drivers. The lack of studies enrolling CMV drivers with MS precludes one from determining whether CMV drivers with this condition are at an increased risk for a motor vehicle crash.

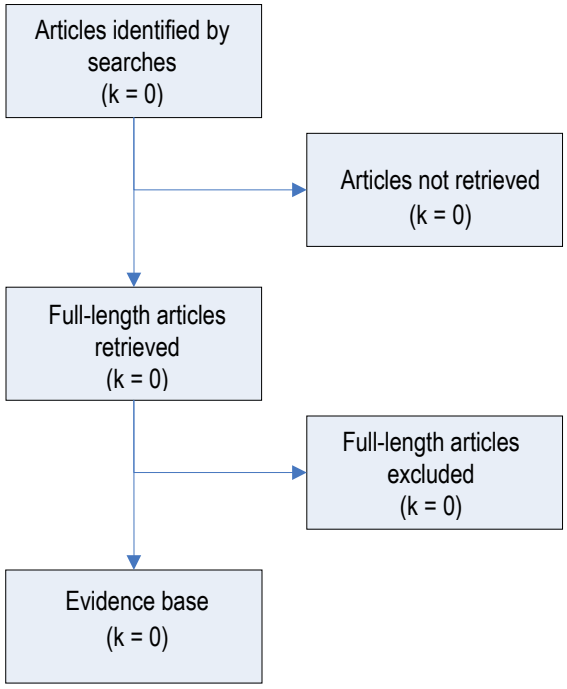
Key Question 4: How frequently should an individual with MS be assessed in order to monitor whether they are safe to drive?

Identification of Evidence Base

The evidence base identification pathway for Key Question 4 is summarized in Figure 22. Our searches[5] identified no articles that were potentially relevant to this key question. Following application of the retrieval criteria for this question (Appendix D), no full-length articles were retrieved and read in full. No retrieved articles were found to meet the inclusion criteria (Appendix D) for this key question.

[5] See Appendix A for search strategies.

Figure 22. Development of Evidence Base for Key Question 4



Section Summary

No evidence was identified regarding assessment time interval for monitoring driver safety in patients with MS. Therefore, no evidence-based conclusion is possible at the present time.

Our searches identified no potentially relevant articles that addressed this question.

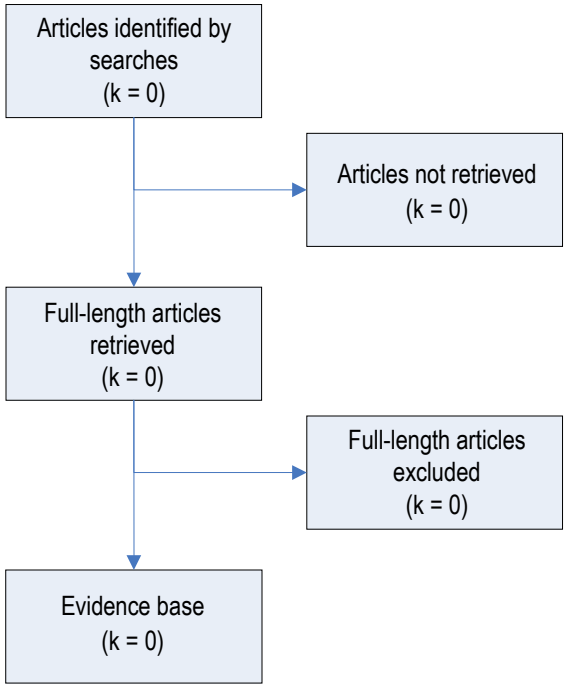
Key Question 5: What is the impact of pharmacotherapy for MS on driver safety?

Identification of Evidence Base

The evidence base identification pathway for Key Question 5 is summarized in Figure 23. Our searches[6] identified no articles that were potentially relevant to this key question. Following application of the retrieval criteria for this question (Appendix D), no full-length articles were retrieved and read in full or met the inclusion criteria (Appendix D) for this key question.

[6] See Appendix A for search strategies.

Figure 23. Development of Evidence Base for Key Question 5



Section Summary

No evidence was identified concerning the relationship between MS pharmacotherapy and driver safety outcomes. Therefore, no evidence-based conclusion is possible at the present time.

Our searches identified no potentially relevant articles that addressed this question.

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Appendix A: Search Summaries

Search Summary for Key Questions 1

The search strategies employed combinations of free text keywords as well as controlled vocabulary terms, including the following concepts. The strategy below is presented in OVID syntax; the search was simultaneously conducted across EMBASE, MEDLINE, and PsycINFO. A parallel strategy was used to search the databases composing the Cochrane Library.

Electronic Database Searches

The following databases have been searched for relevant information.

Name	Date Limits	Platform/Provider
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	1982 through April 23, 2008	OVID
The Cochrane Central Register of Controlled Trials (CENTRAL)	Through 2008, Issue 2	www.thecochranelibrary.com
The Cochrane Database of Methodology Reviews (Methodology Reviews)	Through 2008, Issue 2	www.thecochranelibrary.com
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	Through 2008, Issue 2	www.thecochranelibrary.com
Database of Abstracts of Reviews of Effects (DARE)	Through 2008, Issue 2	www.thecochranelibrary.com
EMBASE (Excerpta Medica)	1980 through April 23, 2008	OVID
Health Technology Assessment Database (HTA)	Through 2008, Issue 2	www.thecochranelibrary.com
MEDLINE	1950 through April 23, 2008	OVID
PreMEDLINE	Searched April 23, 2008	OVID
PsycINFO	Through April 23, 2008	OVID
TRIS	Searched December 11, 2007	
U.K. National Health Service Economic Evaluation Database (NHS EED)	Through 2008, Issue 2	www.thecochranelibrary.com
U.S. National Guideline Clearinghouse™ (NGC)	Searched December 17, 2007	www.ngc.gov

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

Conventions:

OVID

$ = truncation character (wildcard)

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

.de. = limit controlled vocabulary heading

.fs. = floating subheading

.hw. = limit to heading word

.md. = type of methodology (PsycINFO)

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

.pt. = publication Type

.ti. = limit to title

.tw. = limit to title and abstract fields

PubMed

[mh] = MeSH heading

[majr] = MeSH heading designated as major topic

[pt] = Publication Type

[sb] = Subset of PubMed database (PreMEDLINE, Systematic, OldMEDLINE)

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

[tiab] = keyword in title or abstract

[tw] = Text word

Topic-specific Search Terms

Concept	Controlled Vocabulary	Keywords
Parkinson Disease	Exp Parkinson Disease/ Exp Parkinson Disease, Secondary/ Exp Parkinsonian Disorders/	Paralysis Agitans Parkinson Parkinson's Parkinsonian PD fPD sPD
Direct crash risk	Accidents, traffic/ Highway safety Motor traffic accidents Traffic accident Traffic safety	Accident$ Collision$ Crash$ Wreck$
Driving	Exp Car driving/ Driv$.hw. Exp Driving behavior/	Automobile driving Commercial Driving Professional
Motor vehicles	Exp Motor vehicle/ Exp Motor vehicles/	Automobiles Car Haul$ Long distance Truck

CINAHL/EMBASE/MEDLINE/PsycINFO
English language, human

Set Number	Concept	Search Statement
1	Parkinson Disease	exp Parkinson Disease/ or exp Parkinson Disease, Secondary/ or exp Parkinsonian Disorders/ or Parkinson or Parkinson's or Parkinsonian or Paralysis Agitans or PD or fPD or sPD
2	Driving	Automobile driving.de. or exp motor vehicles/ or automobiles.de. or exp driving behavior/ or exp car driving/ or exp motor vehicle/ or (driving or commercial or professional or truck or car or automobile or long distance or haul$).ti.
3	Direct crash risk	(Accidents, traffic/ or highway safety or motor traffic accidents or traffic accident or traffic safety).de. or crash$.ti. or wreck$.ti. or collision.ti. or accident$.ti.
4	Combine sets	1 and (2 or 3)
5	Limit by publication type	4 not ((letter or editorial or news or comment or case reports or note or conference paper).de. or (letter or editorial or news or comment or case reports).pt.)
6	Eliminate overlap	Remove duplicates from 5

Total Identified	Total Downloaded	Total Retrieved	Total Included
123	**92**	**34**	**15**

Search Summary for Key Question 2

Electronic Database Searches

The following databases have been searched for relevant information:

Name	Date Limits	Platform/Provider
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	1982 through April 23, 2008	OVID
The Cochrane Central Register of Controlled Trials (CENTRAL)	Through 2008, Issue 2	www.thecochranelibrary.com
The Cochrane Database of Methodology Reviews (Methodology Reviews)	Through 2008, Issue 2	www.thecochranelibrary.com
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	Through 2008, Issue 2	www.thecochranelibrary.com
Database of Abstracts of Reviews of Effects (DARE)	Through 2008, Issue 2	www.thecochranelibrary.com
EMBASE (Excerpta Medica)	1980 through April 23, 2008	OVID
Health Technology Assessment Database (HTA)	Through 2008, Issue 2	www.thecochranelibrary.com
MEDLINE	1950 through April 23, 2008	OVID
PreMEDLINE	Searched April 23, 2008	OVID
PsycINFO	Through April 23, 2008	OVID
TRIS	Searched December 11, 2007	
U.K. National Health Service Economic Evaluation Database (NHS EED)	Through 2008, Issue 2	www.thecochranelibrary.com
U.S. National Guideline Clearinghouse™ (NGC)	Searched December 17, 2007	www.ngc.gov

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

Conventions:

OVID

$ = truncation character (wildcard)

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

.de. = limit controlled vocabulary heading

.fs. = floating subheading

.hw. = limit to heading word

.md. = type of methodology (PsycINFO)

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

.pt. = publication Type

.ti. = limit to title

.tw. = limit to title and abstract fields

PubMed

[mh] = MeSH heading

[majr] = MeSH heading designated as major topic

[pt] = Publication Type

[sb] = Subset of PubMed database (PreMEDLINE, Systematic, OldMEDLINE)

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

[tiab] = keyword in title or abstract

[tw] = Text word

Topic-specific Search Terms

Concept	Controlled Vocabulary	Keywords
Pharmacotherapy for Parkinson Disease	Exp Antiparkinson Agent/ Exp Parkinson Disease, Secondary/ Exp Parkinsonian Disorders/	Anti Dyskinesia Agent Anti-Dyskinesia Agent Amantadine Apomorphine Bromocriptine Cabergoline Carbidopa Dizocilpine Domperidone Dopamine Receptor Stimulating Agent Efaroxan Entacapone Levodopa Lisuride Modafinil Neurotrophin Pergolide Pramipexole Reboxetine Ropinirole Rotigotine Selegiline
Direct crash risk	Accidents, traffic/ Highway safety Motor traffic accidents Traffic accident Traffic safety	Accident$ Collision$ Crash$ Wreck$
Driving	Exp Car driving/ Driv$.hw. Exp Driving behavior/	Automobile driving Commercial Driving Professional
Motor vehicles	Exp Motor vehicle/ Exp Motor vehicles/	Automobiles Car Haul$ Long distance Truck

CINAHL/EMBASE/MEDLINE/PsycINFO
English language, human

Set Number	Concept	Search Statement
1	Pharmacotherapy for Parkinson Disease	Exp Antiparkinson Agent/ or Anti Dyskinesia Agent or Anti-Dyskinesia Agent or Antiparkinson or Anti-parkinson or Amantadine or Apomorphine or Bromocriptine or Cabergoline or Carbidopa or Dizocilpine or Domperidone or Dopamine Receptor Stimulating Agent or Efaroxan or Entacapone or Levodopa or Lisuride or Modafinil or Neurotrophin or Pergolide or Pramipexole or Reboxetine or Ropinirole or Rotigotine or Selegiline
2	Driving	Automobile driving.de. or exp motor vehicles/ or automobiles.de. or exp driving behavior/ or exp car driving/ or exp motor vehicle/ or (driving or commercial or professional or truck or car or automobile or long distance or haul$).ti.
3	Direct crash risk	(Accidents, traffic/ or highway safety or motor traffic accidents or traffic accident or traffic safety).de. or crash$.ti. or wreck$.ti. or collision.ti. or accident$.ti.
4	Combine sets	1 and (2 or 3)
5	Limit by publication type	4 not ((letter or editorial or news or comment or case reports or note or conference paper).de. or (letter or editorial or news or comment or case reports).pt.)
6	Eliminate overlap	Remove duplicates from 5

Total Identified	Total Downloaded	Total Retrieved	Total Included
37	**37**	**27**	**4**

Search Summary for Key Question 3

Electronic Database Searches

The following databases have been searched for relevant information:

Name	Date Limits	Platform/Provider
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	1982 through April 23, 2008	OVID
The Cochrane Central Register of Controlled Trials (CENTRAL)	Through 2008, Issue 2	www.thecochranelibrary.com
The Cochrane Database of Methodology Reviews (Methodology Reviews)	Through 2008, Issue 2	www.thecochranelibrary.com
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	Through 2008, Issue 2	www.thecochranelibrary.com
Database of Abstracts of Reviews of Effects (DARE)	Through 2008, Issue 2	www.thecochranelibrary.com
EMBASE (Excerpta Medica)	1980 through April 23, 2008	OVID
Health Technology Assessment Database (HTA)	Through 2008, Issue 2	www.thecochranelibrary.com
MEDLINE	1950 through April 23, 2008	OVID
PreMEDLINE	Searched April 23, 2008	OVID
PsycINFO	Through April 23, 2008	OVID
TRIS	Searched December 11, 2007	
U.K. National Health Service Economic Evaluation Database (NHS EED)	Through 2008, Issue 2	www.thecochranelibrary.com
U.S. National Guideline Clearinghouse™ (NGC)	Searched December 17, 2007	www.ngc.gov

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

Conventions:

OVID

$ = truncation character (wildcard)

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

.de. = limit controlled vocabulary heading

.fs. = floating subheading

.hw. = limit to heading word

.md. = type of methodology (PsycINFO)

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

.pt. = publication Type

.ti. = limit to title

.tw. = limit to title and abstract fields

PubMed

[mh] = MeSH heading

[majr] = MeSH heading designated as major topic

[pt] = Publication Type

[sb] = Subset of PubMed database (PreMEDLINE, Systematic, OldMEDLINE)

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

[tiab] = keyword in title or abstract

[tw] = ext word

Topic-specific Search Terms

Concept	Controlled Vocabulary	Keywords
Multiple Sclerosis	Exp Multiple Sclerosis/ Multiple Sclerosis, Chronic Progressive Multiple Sclerosis, Relapsing-Remitting	Chariot Disease Disseminated Sclerosis Insular Sclerosis MS Multiple Sclerosis, Acute Fulminating Sclerosis, Disseminated Sclerosis, Insular Sclerosis, Multiple Sclerosis Multiplex
Direct crash risk	Accident Accident prevention Accidents Accidents, occupational Accidents, traffic Highway safety Motor traffic accidents Occupational health Occupational safety Safety Traffic accident Traffic safety Transportation accidents	Accident$ Citation$ Collision$ Crash$ Ticket$ Wreck$
Driving	Automobile driver examination Automobile driving Car driving Driv$.hw. Driver license Driving ability Driving behavior Drivers	Driver$ Driving[ti] Drive Highway Licens$
Motor vehicles	Automobiles Motor vehicle Motor vehicles	Bus Buses Car Cars Haul Long distance Lorry Lorries Motor$ Semi-trailer$ Truck$1 Vehicle$

CINAHL/EMBASE/MEDLINE/PsycINFO
English language, human

Set Number	Concept	Search Statement
1	Multiple Sclerosis	exp Multiple Sclerosis/ or (Chariot Disease or Disseminated Sclerosis or Insular Sclerosis or MS or Multiple Sclerosis, Acute Fulminating or Multiple Sclerosis, Chronic Progressive or Multiple Sclerosis, Relapsing-Remitting or Sclerosis, Disseminated or Sclerosis, Insular or Sclerosis, Multiple or Sclerosis Multiplex)
2	Driving	(Automobiles or Motor vehicles or Motor vehicle or Automobile driving or Car driving or Driving ability or Driving behavior or Drivers).de. and (driver$ or driving$ or drive or licens$ or highway$ or car or cars or vehicle$ or semi-trailer$ or bus or buses or truck$1 or lorry or lorries or haul or (long adj distance)).ti. and (Automobile driver examination or Licensure or Driver license or Safety or Traffic safety or Highway safety or Occupational safety or Occupational Health or Occupational disease).de
3	Direct crash risk	(accident or accidents or accidents, traffic or traffic accident or motor traffic accidents or accidents, occupational or accident prevention or occupational accident or transportation accidents).de. and ((accident$ adj (car or traffic)) or collision$ or crash$ or wreck$ or citation$ or ticket$)
4	Combine sets	1 and (2 or 3)
5	Limit by publication type	4 not ((letter or editorial or news or comment or case reports or note or conference paper).de. or (letter or editorial or news or comment or case reports).pt.)
6	Eliminate overlap	Remove duplicates from 5

Total Identified	Total Downloaded	Total Retrieved	Total Included
46	**8**	**6**	**4**

Search Summary for Key Question 4

Electronic Database Searches

The following databases have been searched for relevant information:

Name	Date Limits	Platform/Provider
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	1982 through April 23, 2008	OVID
The Cochrane Central Register of Controlled Trials (CENTRAL)	Through 2008, Issue 2	www.thecochranelibrary.com
The Cochrane Database of Methodology Reviews (Methodology Reviews)	Through 2008, Issue 2	www.thecochranelibrary.com
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	Through 2008, Issue 2	www.thecochranelibrary.com
Database of Abstracts of Reviews of Effects (DARE)	Through 2008, Issue 2	www.thecochranelibrary.com
EMBASE (Excerpta Medica)	1980 through April 23, 2008	OVID
Health Technology Assessment Database (HTA)	Through 2008, Issue 2	www.thecochranelibrary.com
MEDLINE	1950 through April 23, 2008	OVID
PreMEDLINE	Searched April 23, 2008	OVID
PsycINFO	Through April 23, 2008	OVID
TRIS	Searched December 11, 2007	
U.K. National Health Service Economic Evaluation Database (NHS EED)	Through 2008, Issue 2	www.thecochranelibrary.com
U.S. National Guideline Clearinghouse™ (NGC)	Searched December 17, 2007	www.ngc.gov

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

Conventions:

OVID

$ = truncation character (wildcard)

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

.de. = limit controlled vocabulary heading

.fs. = floating subheading

.hw. = limit to heading word

.md. = type of methodology (PsycINFO)

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

.pt. = publication Type

.ti. = limit to title

.tw. = limit to title and abstract fields

PubMed

[mh] = MeSH heading

[majr] = MeSH heading designated as major topic

[pt] = Publication Type

[sb] = Subset of PubMed database (PreMEDLINE, Systematic, OldMEDLINE)

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

[tiab] = keyword in title or abstract

[tw] = Text word

Topic-specific Search Terms

Concept	Controlled Vocabulary	Keywords
Multiple Sclerosis		Immunotherapy$ Immunosuppre$ Avonex Betaseron Copaxone Glatiramer acetate Mitoxantrone Natalizumab Novantrone Rebif Tysabri
Disease progression	Exp cohort studies/ Exp disease progression/	compar$ cohort$ course disease$) follow-up follow up histor$ longitudinal$ multivariate natural$ prognosis outcome$ predict$ progress$ prospective$ reproducib$
Direct crash risk	Accidents, traffic/ Highway safety Motor traffic accidents Traffic accident Traffic safety	Accident$ Collision$ Crash$ Wreck$
Driving	Exp Car driving/ Driv$.hw. Exp Driving behavior/	Automobile driving Commercial Driving Professional
Motor vehicles	Exp Motor vehicle/ Exp Motor vehicles/	Automobiles Car Haul$ Long distance Truck

CINAHL/EMBASE/MEDLINE/PsycINFO
English language, human

Set Number	Concept	Search Statement
1	Multiple Sclerosis	Exp Multiple Sclerosis/ or (Chariot Disease or Disseminated Sclerosis or Insular Sclerosis or MS or Multiple Sclerosis, Acute Fulminating or Multiple Sclerosis, Chronic Progressive or Multiple Sclerosis, Relapsing-Remitting or Sclerosis, Disseminated or Sclerosis, Insular or Sclerosis, Multiple or Sclerosis Multiplex)
2	Disease progression	Exp disease progression/ or exp cohort studies/ or (prognosis or outcome$ or follow-up or predict$) or ((natural$ or disease$) adj (progress$ or course$ or histor$)) or (cohort$ or compar$ or longitudinal$ or prospective$ or multivariate or reproducib$ or follow up or follow-up)
3	Driving	Automobile driving.de. or exp motor vehicles/ or automobiles.de. or exp driving behavior/ or exp car driving/ or exp motor vehicle/ or (driving or commercial or professional or truck or car or automobile or long distance or haul$).ti.
4	Combine sets	1 and 2 and 3
5	Limit by publication type	7 not ((letter or editorial or news or comment or case reports or note or conference paper).de. or (letter or editorial or news or comment or case reports).pt.)
6	Eliminate overlap	Remove duplicates from 8

Total Identified	Total Downloaded	Total Retrieved	Total Included
7	**1**	**0**	**0**

Search Summary for Key Question 5

Electronic Database Searches

The following databases have been searched for relevant information:

Name	Date Limits	Platform/Provider
CINAHL (Cumulative Index to Nursing and Allied Health Literature)	1982 through April 23, 2008	OVID
The Cochrane Central Register of Controlled Trials (CENTRAL)	Through 2008, Issue 2	www.thecochranelibrary.com
The Cochrane Database of Methodology Reviews (Methodology Reviews)	Through 2008, Issue 2	www.thecochranelibrary.com
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	Through 2008, Issue 2	www.thecochranelibrary.com
Database of Abstracts of Reviews of Effects (DARE)	Through 2008, Issue 2	www.thecochranelibrary.com
EMBASE (Excerpta Medica)	1980 through April 23, 2008	OVID
Health Technology Assessment Database (HTA)	Through 2008, Issue 2	www.thecochranelibrary.com
MEDLINE	1950 through April 23, 2008	OVID
PreMEDLINE	Searched April 23, 2008	OVID
PsycINFO	Through April 23, 2008	OVID
TRIS	Searched December 11, 2007	
U.K. National Health Service Economic Evaluation Database (NHS EED)	Through 2008, Issue 2	www.thecochranelibrary.com
U.S. National Guideline Clearinghouse™ (NGC)	Searched December 17, 2007	www.ngc.gov

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

Conventions:

OVID

$ = truncation character (wildcard)

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

.de. = limit controlled vocabulary heading

.fs. = floating subheading

.hw. = limit to heading word

.md. = type of methodology (PsycINFO)

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

.pt. = publication Type

.ti. = limit to title

.tw. = limit to title and abstract fields

PubMed

[mh] = MeSH heading

[majr] = MeSH heading designated as major topic

[pt] = Publication Type

[sb] = Subset of PubMed database (PreMEDLINE, Systematic, OldMEDLINE)

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

[tiab] = keyword in title or abstract

[tw] = Text word

Topic-specific Search Terms

Concept	Controlled Vocabulary	Keywords
Multiple Sclerosis		Immunotherapy$ Immunosuppre$ Avonex Betaseron Copaxone Glatiramer acetate Mitoxantrone Natalizumab Novantrone Rebif Tysabri
Direct crash risk	Accidents, traffic/ Highway safety Motor traffic accidents Traffic accident Traffic safety	Accident$ Collision$ Crash$ Wreck$
Driving	Exp Car driving/ Driv$.hw. Exp Driving behavior/	Automobile driving Commercial Driving Professional
Motor vehicles	Exp Motor vehicle/ Exp Motor vehicles/	Automobiles Car Haul$ Long distance Truck

CINAHL/EMBASE/MEDLINE/PsycINFO
English language, human

Set Number	Concept	Search Statement
1	Multiple Sclerosis	exp Multiple Sclerosis/ or (Chariot Disease or Disseminated Sclerosis or Insular Sclerosis or MS or Multiple Sclerosis, Acute Fulminating or Multiple Sclerosis, Chronic Progressive or Multiple Sclerosis, Relapsing-Remitting or Sclerosis, Disseminated or Sclerosis, Insular or Sclerosis, Multiple or Sclerosis Multiplex)
2	Driving	Automobile driving.de. or exp motor vehicles/ or automobiles.de. or exp driving behavior/ or exp car driving/ or exp motor vehicle/ or (driving or commercial or professional or truck or car or automobile or long distance or haul$).ti.
3	Direct crash risk	(Accident or accidents or accidents, traffic or traffic accident or motor traffic accidents or accidents, occupational or accident prevention or occupational accident or transportation accidents).de. and ((accident$ adj (car or traffic)) or collision$ or crash$ or wreck$ or citation$ or ticket$)
4	Combine sets	or/1-3
5	Limit by publication type	4 not ((letter or editorial or news or comment or case reports or note or conference paper).de. or (letter or editorial or news or comment or case reports).pt.)
6	Eliminate overlap	Remove duplicates from 5

Total Identified	Total Downloaded	Total Retrieved	Total Included
0	0	0	0

Appendix B: Retrieval Criteria

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

Retrieval Criteria for Key Question 1

- 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 PD or a study that attempted to evaluate the relationship between PD and the following direct and indirect measures of driver safety:
    - Crash
    - Measures of driving-related performance (laboratory and experimental)
- Article must describe a study that includes a comparison group comprising comparable individuals who do not have PD.

Retrieval Criteria for Key Question 2

- Article must have been published in the English language.
- Article must have enrolled 10 or more individuals.
- Article may describe a study that attempted to evaluate the relationship between PD and the following direct and indirect measures of driver safety:
    - Crash
    - Measures of driving-related performance (laboratory and experimental)
    - Measures of driving-related cognitive function
    - Measures of driving-related psychomotor function
- Article may describe a study that includes a comparison group comprising comparable individuals who were not taking pharmacotherapy for PD.

Retrieval Criteria for Key Question 3

- Article must have been published in the English language.
- Article must have enrolled 10 or more individuals.
- Article must describe a study that includes a comparison group comprising comparable individuals who do not have MS, or describe an analysis of risk factors that may affect driver safety among individuals with MS.
- Article must describe a study that attempted to evaluate the relationship between MS and one of the following direct and indirect measures of driver safety:
    - Crash
    - Measures of driving-related performance (laboratory and experimental)

Retrieval Criteria for Key Question 4

- Article must have been published in the English language.
- Article must have enrolled 10 or more individuals.
- Article may describe a study that attempted to evaluate the relationship between MS and the following direct and indirect measures of driver safety:
  - Crash
  - Measures of driving-related performance (laboratory and experimental)
- Article must describe a study that includes a dichotomous comparison comprising comparable individuals who do not have MS.

Retrieval Criteria for Key Question 5

- Article must have been published in the English language.
- Article must have enrolled 10 or more individuals.
- Article may describe a study that attempted to evaluate the relationship between MS and the following direct and indirect measures of driver safety:
  - Crash
  - Measures of driving-related performance (laboratory and experimental)
  - Measures of driving-related cognitive or psychomotor function deficits
  - Measure of daytime sleepiness
- Article must describe a study that includes a comparison group comprising individuals who were not taking pharmacotherapy for MS.

Appendix C: Inclusion Criteria

Appendix C lists the inclusion criteria for each of the six key questions addressed in this evidence report.

Inclusion Criteria for Key Question 1

- 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, including 10 or more individuals in each group for comparison.
- 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 PD or a study that attempted to evaluate the relationship between PD and the following direct and indirect measures of driver safety:
  - Crash
  - Measures of driving-related performance (laboratory and experimental)
- Article may compare the proportion of drivers with PD who crashed with the proportion of comparable individuals without the disorder who did not crash.
- Article may compare proportion of individuals with PD who crashed to those in the general population who experienced crash.
- Studies that evaluated both PD and other neurological disorders among individuals were included as long as the PD 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 ECRI Institute to calculate (directly or through imputation) effect size estimates and confidence intervals.
- Article must describe a dichotomous comparison between individuals with PD based on the outcome.

Inclusion Criteria for Key Question 2

- 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, including 10 or more individuals in each group for comparison.
- Article must have enrolled individuals aged ≥18.

- Article must have enrolled individuals who were administered pharmacotherapy that is currently available in the United States which is not combined or supplemented by pharmacotherapy not presently available in the United States.
- Article may describe a study that attempted to evaluate the relationship between PD and the following direct and indirect measures of driver safety:
  - Crash
  - Measures of driving-related performance (laboratory and experimental)
  - Measures of driving-related cognitive or psychomotor function deficits
  - Measures of daytime sleepiness or comparable sleep condition affecting driver safety
- Article must describe a study that includes a comparison group comprising comparable individuals who are not taking study medication (e.g., placebo group).
- Article may describe a study that includes a comparison group comprised of comparable individuals who do not have PD.
- 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.

Inclusion Criteria for Key Question 3

- 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 MS or describe an analysis of risk factors that may affect driver safety among individuals with MS.
- Article must describe a study that attempted to evaluate the relationship between MS and one of the following direct and indirect measures of driver safety:
  - Crash
  - Measures of driving-related performance (laboratory and experimental)
- Article may compare the proportion of drivers with MS who crashed with the proportion of comparable individuals without the disorder who did not crash.
- Article may compare proportion of individuals with MS who crashed to those in the general population who experienced crash.
- Studies that evaluated both MS and other neurological disorders among individuals were included as long as the MS 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 ECRI Institute to calculate (directly or through imputation) effect size estimates and confidence intervals.

Inclusion Criteria for Key Question 4

- 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 have enrolled patients in which MS was diagnosed through valid test assessment and clinically confirmed.
- Article may describe a study that attempted to evaluate the relationship between MS and the following direct and indirect measures of driver safety:
  - Crash
  - Measures of driving-related performance (laboratory and experimental)
- Article must describe a study that includes a comparison group comprising comparable individuals who do not have MS.

Inclusion Criteria for Key Question 5

- 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 may describe a study that attempted to evaluate the relationship between MS and the following direct and indirect measures of driver safety:
  - Crash
  - Measures of driving-related performance (laboratory and experimental)
  - Measures of driving-related cognitive function
  - Measures of driving-related psychomotor function
- Article must describe a study that includes a comparison group comprising comparable individuals who do not have MS

Appendix D: Excluded Articles

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

Reference	Year	Reason for Exclusion
Bacon et al.(143)	2007	No relevant outcome data
Bloxham et al.(144)	1987	No dichotomous comparison based on the outcome
Borromei et al.(145)	1999	No dichotomous comparison based on the outcome
Factor et al.(146)	1990	No relevant outcome data
Grace et al.(147)	2005	n <10 in comparison group
Harvard Medical School(148)	2002	Editorial; background information
Lachenmayer et al.(149)	2000	Background information article
Lings et al.(150)	1992	No relevant outcome data
Madeley et al.(151)	1990	n <10 in potential groupings for dichotomous comparison
Olanow et al.(152)	2000	Review
Ondo et al.(153)	2001	No relevant outcome data
Poser et al.(154)	1993	Background information article
Radford et al.(155)	2004	n <10 in comparison group
Rye et al.(156)	2000	No relevant outcome data
Shrag(157)	2005	Editorial
Stolwyk et al.(158)	2006	No attempt to associate prognostic factors with driving outcomes.
Tan et al.(159)	2002	No relevant outcome data
Tandberg et al.(160)	1998	Background information article; no relevant outcome data
Van Hilten et al.(161)	1993	No relevant outcome data

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

Reference	Year	Reason for Exclusion
Amick et al.(113)	2007	<10 group participants with outcome for comparison
Boyle et al.(162)	2005	Review
Barbeau et al.(163)	1969	Review
Comella et al.(164)	2002	Editorial
Cotzias et al.(165)	1969	Pharmacotherapy not presently available in the United States.
Gull(166)	2006	Background information
Hauser et al.(167)	2000	No clear inclusion of a comparison group comprised of comparable individuals who are not taking study medication (i.e., placebo group) in reporting of results
Homann et al.(112)	2002	Review
Homann et al.(168)	2003	Review
Lesser et al.(169)	1979	Pharmacotherapy not presently available in the United States.
Lowe et al.(170)	1998	Editorial
Mars et al.(171)	1972	Pharmacotherapy not presently available in the United States.
Ondo et al.(153)	2001	Pharmacotherapy not presently available in the United States analyzed together with pharmacotherapy that is presently available.
Pal et al.(172)	2001	Pharmacotherapy combined with drug not presently available in the United States
Paus et al.(173)	2003	Pharmacotherapy combined with drug not presently available in the United States
Rascol et al.(174)	2000	Pharmacotherapy combined with drug not presently available in the United States
Razmy et al.(175)	2004	No control group for comparison (presented treatment group data only)
Schapira et al.(176)	2000	Case series study; <10 group participants with outcome
Scheife et al.(177)	2000	Review
Schlesinger et al.(178)	2003	Crash data for control group not reported; Sleepiness data does not include comparison group not taking drug.
Tanner et al.(114)	2000	Editorial
Uitti et al.(179)	2003	Background information
Verster et al.(180)	2003	No relevant outcome data

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

Reference	Year	Reason for Exclusion
Chipchase(181)	2003	No relevant outcome data
Shawaryn(182)	2002	No control group for outcome comparison

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

As stated in the main text, ECRI Institute evidence reports differ substantially from other systematic reviews in that we provide two types of conclusion: qualitative conclusions and quantitative conclusions. In order to reach these conclusions, we use an algorithm developed by ECRI Institute to guide the conduct and interpretation of the analyses performed during the development of this evidence report.(62) The algorithm, which is presented in Figure E-2 through Figure E-5, formalizes the process of systematic review by breaking the process down into several discrete steps. At each step, rules are applied that determine the next step in the systematic review process and ultimately to the stability and strength of evidence ratings that are allocated to our conclusions. Because the application of the rules governing each step in the algorithm (henceforth called a decision point) guide the conduct of the systematic review process and how its findings are interpreted, much time and effort was spent in ensuring that the rules and underlying assumptions for each decision point were reasonable.

The algorithm is comprises three distinct sections: a *General* section, a *Quantitative* section, and a *Qualitative* section. The system employs 14 decision points (Table 46). Four of them are listed in the General section because they apply to both quantitative conclusions as well as qualitative conclusions. The other 10 apply specifically to either quantitative conclusions (Decision Points 5-9) or qualitative conclusions (Decision Points 10-14). The rest of this appendix defines these decision points and describes how we resolved them for this report. After these descriptions, the pathways for the full system appear in Figure E-2 through Figure E-5.

Note that we applied this system separately for each outcome of interest. This is because many aspects of the evidence (quality, consistency, etc.) can vary by outcome.

Table 46. Decision Points in the ECRI Institute System

Category	Decision Point
General	1) What is the quality of individual studies?
	2) What is the overall quality of evidence?
	3) Is a quantitative estimate potentially appropriate?
	4) Are data informative?
Quantitative	5) Are data quantitatively consistent (homogeneous)?
	6) Are findings stable (quantitatively robust)?
	7) Are there sufficient data to perform meta-regression?
	8) Does meta-regression explain heterogeneity?
	9) Is the meta-regression model robust?
Qualitative	10) Are data qualitatively robust?
	11) Is meta-analysis possible?
	12) Are data qualitatively consistent?
	13) Was at least one study a multicenter study?
	14) Is the magnitude of effect extremely large?

Decision Point 1: Acceptable Quality?

Decision Point 1 serves two purposes: 1) to assess the quality of each included study; 2) to provide a means of excluding studies that are so prone to bias that their reported results cannot be considered useful. To aid in assessing the quality of each of the studies included in this evidence report, we used two study quality assessment instruments. The choice of which instrument to use was based on the design of the study used to address the key questions of interest. In this evidence report we used two revised versions of the Newcastle-Ottawa Quality Assessment Scale (one for case-control studies, one for cohort studies).(142) These instruments are presented in Appendix F. To assess the quality of an individual study, we computed a normalized score so that a perfect study received a score of 10, a study for which the answers to all items were "No" received a score of 0, and a study for which the answers to all questions were "NR" was 5. Quality scores were converted to categories as shown in Table 14 (see Methods section of main document). The definitions for what constitutes low-, moderate-, or high-quality evidence were determined *a priori* by a committee of four methodologists. Because the quality was determined separately for each outcome, a study that scored as high quality for one outcome might score as moderate or low quality for another outcome.

Decision Point 2: Determine Quality of Evidence Base

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

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

Category	Median EQS I Score	Median NOQAS Score (case-control or cohort)	Median EQS VI Score
High Quality	≥9.0		
Moderate Quality	6.0 to 8.9	≥8.0	≥8.0
Low Quality	≤6.0	<8.0	<8.0

EQS = ECRI Institute quality scale
NOQAS = Newcastle-Ottawa quality assessment scale

Decision Point 3: Is a Quantitative Analysis Potentially Appropriate?

The answer to Decision Point 3 depends upon the adequacy of reporting in available studies as well as the number of available studies. In order to permit a quantitative estimate of an effect size for a given outcome, the data for that outcome must be reported in at least three studies in a manner that allows the data to be pooled in a meta-analysis. If less than three studies are available, no quantitative estimate is usually appropriate, regardless of reporting. Another situation that does not permit a quantitative estimate is when at least three studies are relevant to the general topic, but fewer than 75% of them reported the outcome and as well as sufficient information for determination of the effect size and its dispersion, either by direct reporting from the trial or calculations based on reported information. If no quantitative estimate would be appropriate, then one moves directly to Decision Point 10 to determine whether the evidence supports a qualitative conclusion.

Decision Point 4: Are Data Informative?

When there are only a small number of patients in an evidence base, statistical tests generally do not perform well. Under such circumstances, statistics cannot determine whether a true difference exists between treatments. This means that no clear conclusion can be drawn. For this decision point, we determined whether the precision of an evidence base was sufficient to permit a conclusion. Statistically significant results are informative because they mean that a treatment effect may exist. Statistically nonsignificant results are also potentially informative, but only if they exclude the possibility that a clinically significant treatment effect exists.

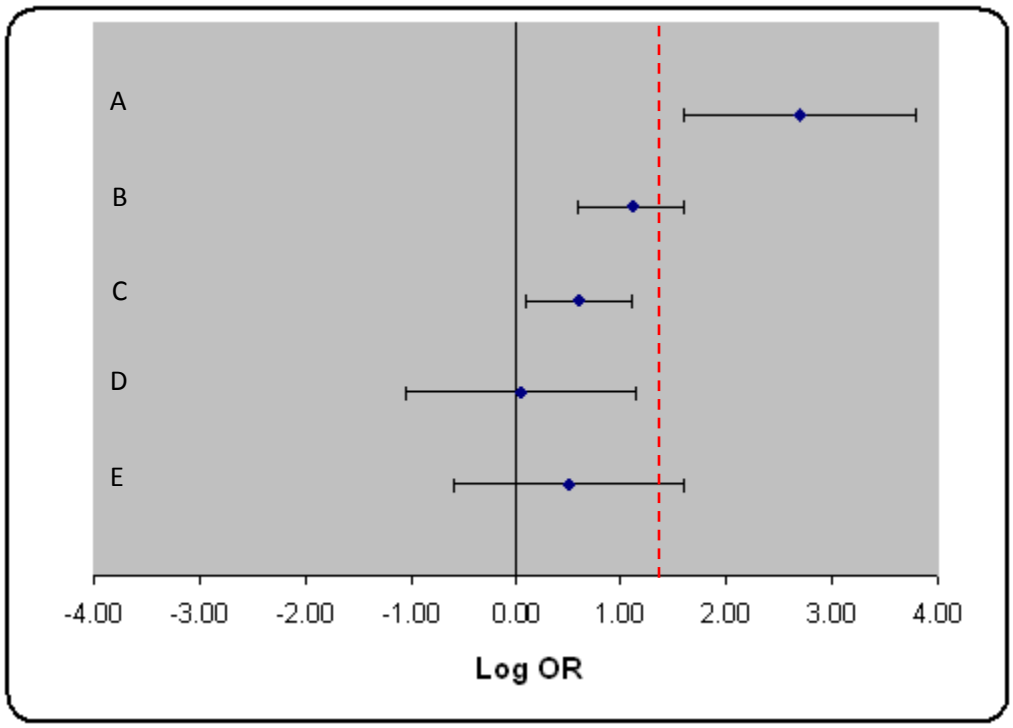
When a meta-analysis is performed, a key concern is the confidence interval around the random-effects summary statistic. If this interval is so wide that it is includes a clinically significant (or substantial) effect in one direction *and also an effect in the opposite direction*, then the evidence is inconclusive, and therefore uninformative.(183)

Thus, when considering the summary effect size from a meta-analysis (or the effect size from a single study), there are three ways in which the effect can be "informative":

1) The effect size is statistically significantly different from 0. This would be indicated whenever the confidence interval does not overlap 0.
2) The confidence interval is narrow enough to exclude the possibility that a *clinically significant difference* exists.
3) The confidence interval is narrow enough to exclude the possibility that a *substantial difference* exists. This possibility is included to address situations when even a very small effect can be considered "clinically significant" (e.g., a difference in mortality rates), but the effect may not be "substantial".

Consider Figure E-1. Four of the findings in this figure are informative (A to D). Only finding E is noninformative.

Figure E-1.Informative Findings



Dashed Line = Threshold for a clinically significant difference

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

Note that when the evidence base consists of one or two studies, and the only usable data from one study consists of a p-value that was calculated using the wrong statistical test, then the data cannot generally be considered "informative." If, however, the study reported sufficient information for one to perform the correct test, then informativeness can be determined.

Decision Point 5: Are Data Quantitatively Consistent (Homogeneous)?

This decision point was used only when the answer to Decision Point 3 was affirmative and a quantitative analysis was performed. Quantitative consistency refers to the extent to which the quantitative results of different studies are in agreement. The more consistent the evidence, the more precise a summary estimate of treatment effect derived from an evidence base will be. Quantitative consistency refers to consistency tested in a meta-analysis using a test of homogeneity. For this

evidence report, we used Higgins and Thompson's I^2 statistic.(75) By convention, we considered an evidence base as being quantitatively consistent when I^2 <50%.

If the findings of the studies included were homogeneous (I^2 <50%), we obtained a summary effect size estimate by pooling the results of these studies using random-effects meta-analysis (REMA). If the findings were not homogeneous, we moved on to Decision Point 7 (exploration of heterogeneity, if ≥10 studies) or Decision Point 9 (qualitative analysis).

Decision Point 6: Are Findings Stable (Quantitatively Robust)?

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

We utilize three different sensitivity analyses. These sensitivity analyses are:

1. *Removal of one study and repeat meta-analysis.* The purpose of this sensitivity analysis is to determine whether a meta-analysis result is driven by a particular trial. For example, a large trial may have a very strong impact on the results of a meta-analysis because of its high weighting.
2. *Publication bias test.* The publication bias test used (if appropriate) in this evidence report is that of Duval and Tweedie.(89-91,184) Based on the degree of asymmetry in a funnel plot constructed from the findings of the included studies, this test(90,91)estimates the number of unpublished studies (and their effect sizes). After addition of any "missing" data to the original meta-analysis, the overall effect size is estimated again. If evidence of publication bias was identified and the summary effect size estimate, adjusted for "missing" studies, differed from the pooled estimate of treatment effect determined by the original fixed-effects meta-analysis by >±5%, we determined that the findings of our original analysis are not robust and the effect size estimate is not stable. This test is not appropriate if there are <10 studies in a meta-analysis.
3. *Cumulative REMA.* Cumulative meta-analysis provides a means by which one can evaluate the effect of the size of the evidence base (in terms of the number of individuals enrolled in the included studies and the number of included studies) on the stability of the calculated effect-size estimate. We typically perform two different cumulative REMAs:
    a. Studies are added cumulatively to a REMA by date of publication-oldest study first.
    b. Studies are added cumulatively to a REMA by date-newest study first.

    In each instance, the pooled effect-size estimate was considered unstable if any of the last three studies to be added resulted in a change in the cumulative summary effect-size estimate effect of >±5%. This test is not appropriate if all studies in a meta-analysis have the same publication date (as was the case in the only meta-analyses performed in this report).

The prespecified tolerance levels for each of the potential effect-size estimates we could have utilized in this evidence report are presented in Table E-2.

Table E-2. Prespecified Tolerance Levels

Effect Size Estimate	WMD	SMD	% of Individuals	RR	OR
Tolerance	±5%	±0.1	±5%	±0.05	±0.05

Since the nature of the evidence bases precluded quantitative analysis, stability of findings could not be assessed in this report.

Decision Point 7: Are There Sufficient Data to Perform Meta-regression?

We required a minimum of 10 studies before attempting meta-regression.

Decision Points 8 and 9: Exploration of Heterogeneity

We will always attempt to determine the source of heterogeneity when the evidence base consists of 10 or more studies using meta-regression. In preparing this evidence report, we did not encounter any situations in which we had a heterogeneous evidence base consisting of at least 10 studies. Consequently, Decision Points 8 and 9 are irrelevant to the present report and we do not discuss them further.

Decision Point 10: Are Qualitative Findings Robust?

Decision Point 10 allows one to determine whether the qualitative findings of two or more studies can be overturned by sensitivity analysis. The same sensitivity analyses used to test quantitative robustness were used to test qualitative robustness. We considered our qualitative findings to be overturned only when the sensitivity analyses altered our qualitative conclusion (i.e., a statistically significant finding became nonsignificant as studies were added to the evidence base). Otherwise, we concluded that our qualitative findings were robust.

Decision Point 11: Is Meta-analysis Possible?

This Decision Point is used only when the evidence base for an outcome consists of two studies.

A meta-analysis is possible if each study reports an effect size and its standard error, or if each study reports sufficient information for the reader to calculate these values. Note that meta-analysis is never appropriate if two studies have statistically significant effect sizes in opposite directions.

Decision Point 12: Are Data Qualitatively Consistent?

This Decision Point is used only when the evidence base for an outcome consists of two studies.

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

Decision Point 13: Is at Least One Study a Multicenter Study?

Multicenter trials may increase the strength of a one- or two-study evidence base because they demonstrate partial replication of findings; they have shown that different investigators at different centers can obtain similar results using the same protocol. We defined a multicenter trial as any trial that met the following two conditions: 1) ≥3 centers and 2) either ≥100 patients or at least 3 centers enrolled ≥20 patients/center.

Decision Point 14: Is Magnitude of Treatment Effect Large?

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

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

Additional Consideration: Evidence from Indirect or Surrogate Outcomes

In certain instances when an evidence base includes only one or two studies with direct evidence (e.g., crash data), the strength of evidence may be increased by additional studies of indirect outcomes (e.g., driving simulator tests, visual function tests) that show findings consistent with the direct evidence study findings.

Figure E-2. General Section

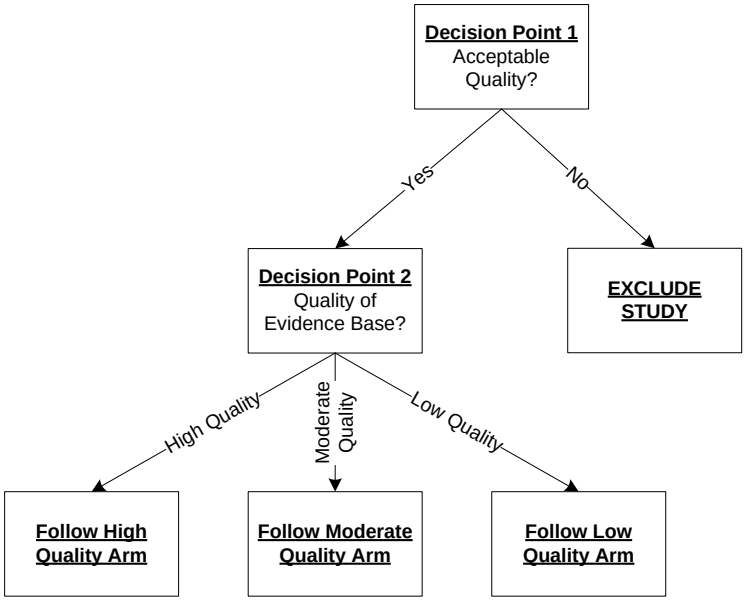


Figure E-3. High-quality Pathway

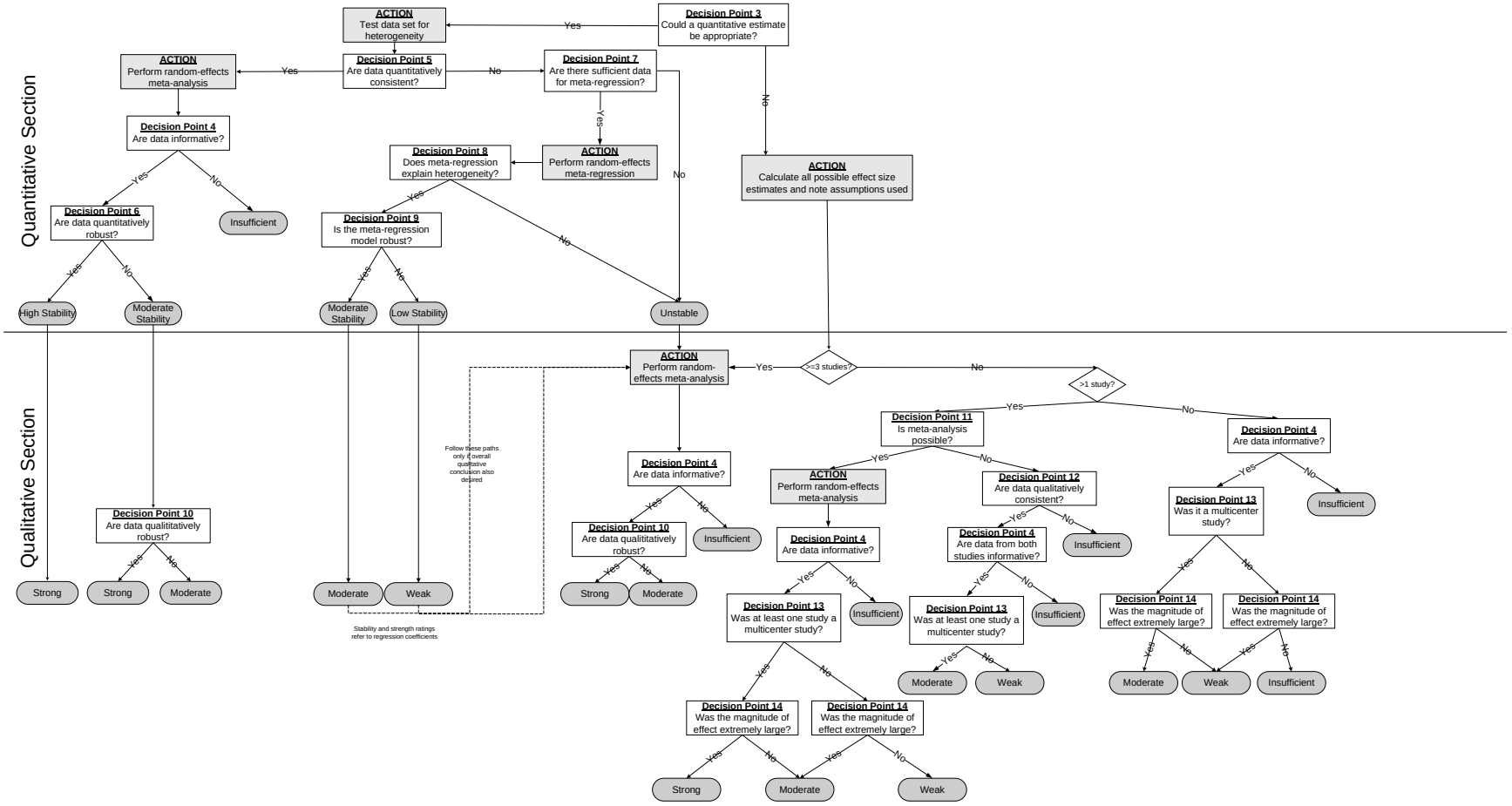


Figure E-4. Moderate-quality Pathway

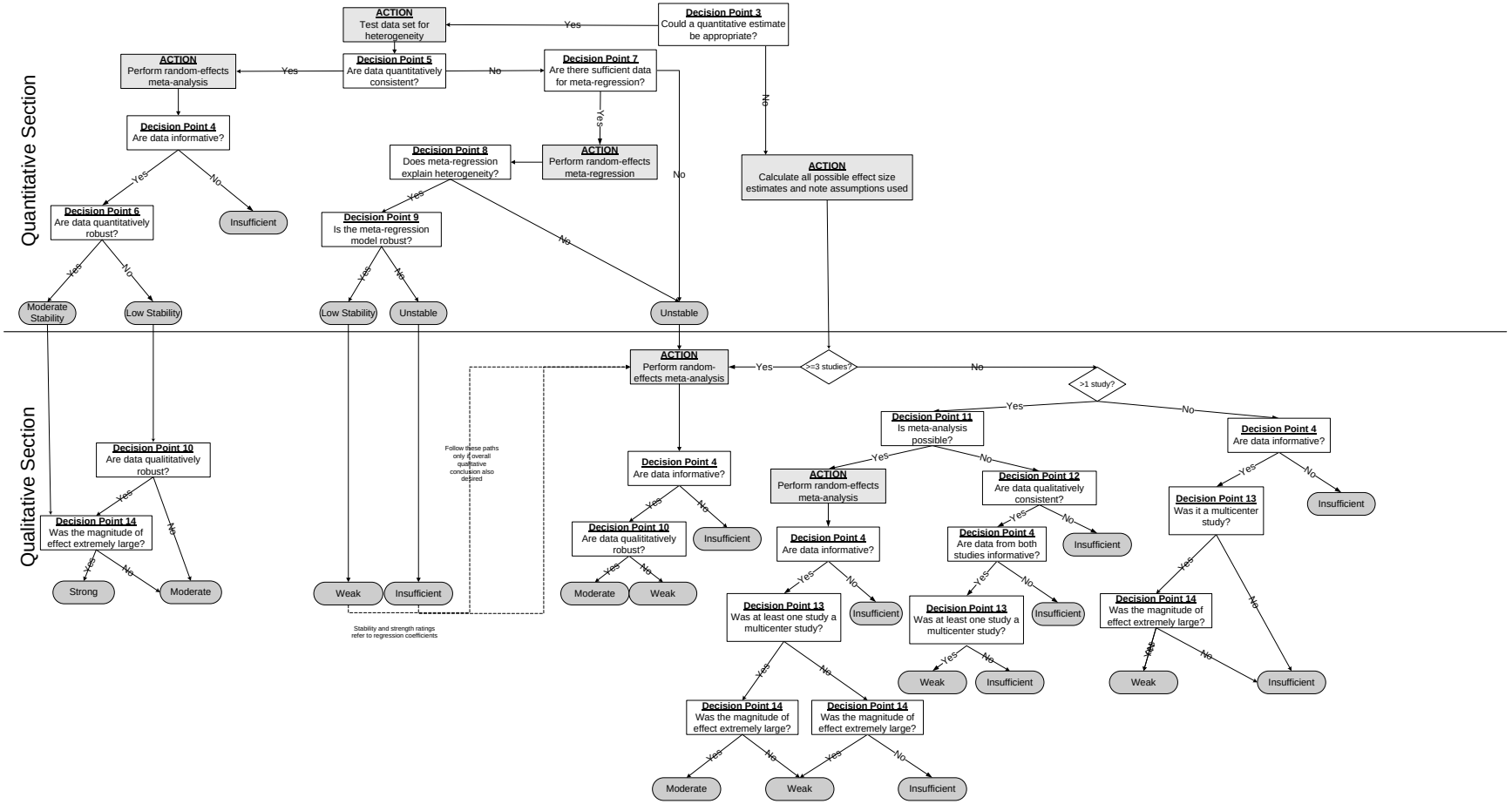
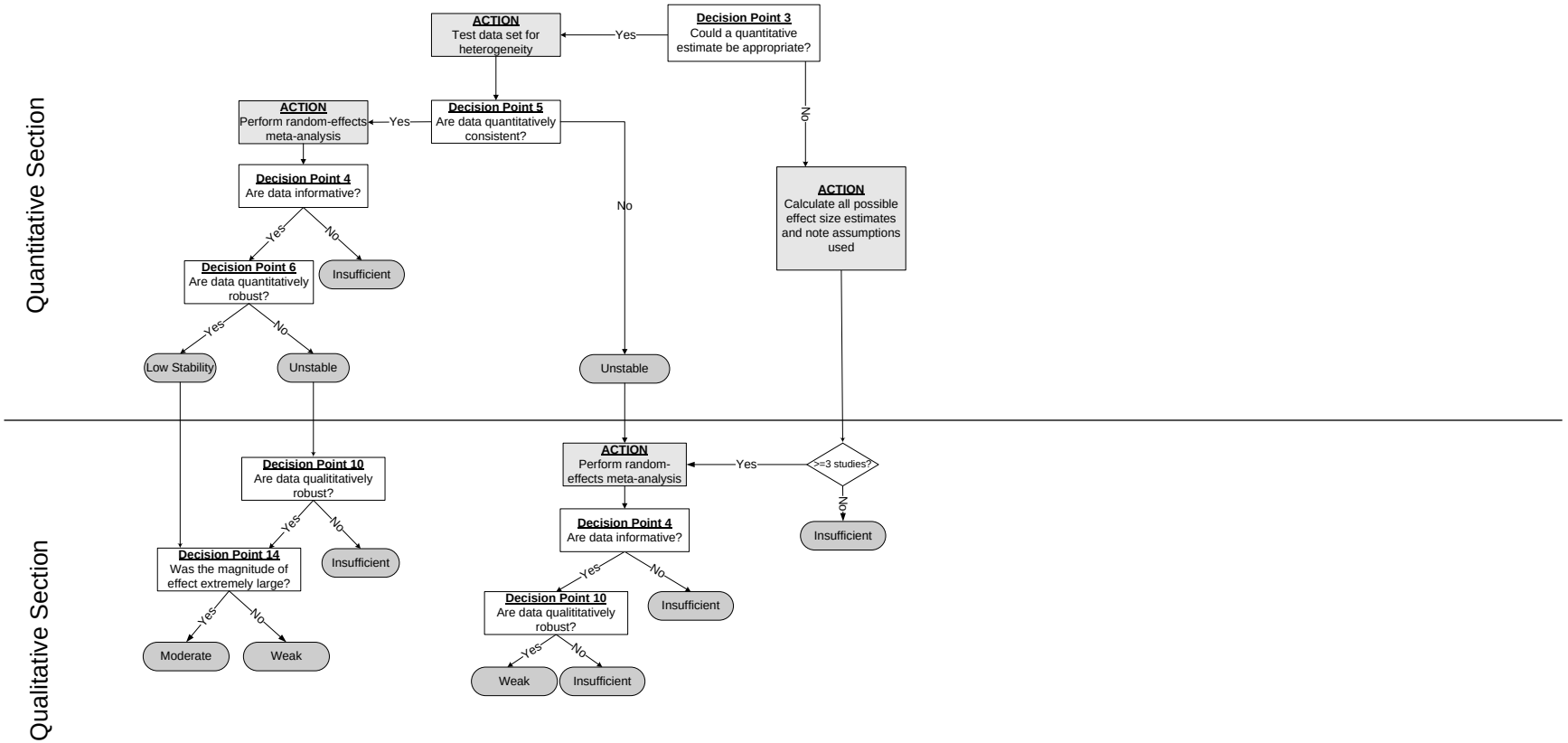


Figure E-5. Low-quality Pathway



Appendix F: Quality Assessment Instruments Used

Three different assessment instruments were used to assess the quality of the studies included in the evidence bases for the key questions addressed in this evidence report. One is a revised version of the Newcastle-Ottawa Quality Assessment Scale for cohort studies.(142) The remaining two are the ECRI Institute quality scales for controlled trials and survey studies.

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?

ECRI Institute Quality Scale I: Controlled Trials

Question #	Question
1	Were patients randomly assigned to the study's groups?
2	Did the study use appropriate randomization methods?
3	Was there concealment of group allocation?
4	For nonrandomized trials, did the study employ any other methods to enhance group comparability?
5	Were patients assigned to groups based on factors other than patient or physician preference?
6	Did patients in the different study groups have similar levels of performance on the outcome of interest at the time they were assigned to groups?
7	Were the study groups comparable for all other important factors at the time they were assigned to groups?
8	Did the study enroll all suitable patients or consecutive suitable patients within a time period?
9	Was the comparison of interest prospectively planned?
10	If patients received ancillary treatment(s), was there a ≤5% difference between groups in the proportion of patients receiving each specific ancillary treatment?
11	Were all of the study's groups concurrently treated?
12	Was compliance with treatment ≥85% in both of the study's groups?
13	Were subjects blinded to the treatment they received?
14	Was the healthcare provider 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 the integrity of blinding of patients, physicians or outcome raters tested and found to be preserved?
17	Was the outcome measure of interest objective **and** objectively measured?
18	Was the instrument used to measure the outcome standard?
19	Was there ≤15% difference in the length of follow-up for the two groups?

Question #	Question
20	Did ≥85% of the patients complete the study?
21	Was there a ≤15% difference in completion rates in the study's groups?
22	Was the funding for this study derived from a source that does not have a financial interest in its results?

ECRI Institute Quality Scale VI: Surveys

Item	Question
1	Were the questions developed from an expert group or focus group?
2	Was the pretest sample sufficiently large (>40 respondents)?
3	Were the characteristics of those who did not complete the study compared with those who completed the study, and were those characteristics similar?
4	Were the pretest sample respondents similar in characteristics to the study's respondents?
5	Were the respondents selected for the survey either consecutively or randomly?
6	Are the questions about crash (or other relevant outcome) not in the first 25% of the questions?
7	Does the questionnaire have reliability checks by asking the same question more than once but differently?
8	Were the respondents informed that their responses were confidential?
9	Were the conclusions as stated in the abstract and discussion consistent with the data presented in the results section?
10	Was the funding for this study derived from a source that does not have a financial interest in its results?

Appendix G: Quality Score Tables

Key Question 1

Table G-1. Quality Assessment Table for Cohort Studies

Reference	Items										Quality Category
	1	2	3	4	5	6	7	8	9	10	
Dubinsky et al.(99)	Y	Y	Y	N	N	N	Y	Y	Y	Y	Low
Adler et al.(98)	Y	S	N	Y	Y	N	Y	Y	NR	Y	Low
Hobson et al.(100)	Y	Y	N	Y	N	N	Y	Y	NR	Y	Low
Devos et al.(101)	Y	S	Y	Y	Y	Y	Y	Y	NR	Y	Moderate
Singh et al.(102)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Moderate
Uc et al.(103-105)	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Moderate
Stolwyk et al.(106,107)	Y	S	Y	Y	Y	Y	Y	Y	NR	Y	Moderate
Worringham et al.(108) Wood et al.(109)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Moderate
Zesiewicz et al.(110)	Y	N	S	Y	N	Y	Y	Y	NR	Y	Low
Heikkila et al. (143)	Y	N	N	Y	Y	N	Y	Y	NR	Y	Low

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

Table G-2. Quality Assessment Table for Survey Studies

Reference	Items										Quality Category
	1	2	3	4	5	6	7	8	9	10	
Meindorfner et al.(97)	N	NR	NR	NR	Y	Y	Y	Y	Y	NR	Low

N = No
NR = Not reported
Y = Yes

Key Question 2

Table G-3. Quality Assessment Table for 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	
Sethi et al.(129)	N	N	N	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	N	Moderate
Adler et al.(95)	Y	NR	NR	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N	N	Moderate
Parkinson Study Group et al.(130)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	NR	N	Y	Y	Y	N	N	High
Shannon et al.(131)	Y	Y	NR	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	NR	NR	NR	N	Y	Y	N	Y	N	Moderate

N = No
NR = Not reported
Y = Yes

Key Question 3

Table G-4. Quality Assessment Table for Cohort Studies

Reference	Items										Quality Category
	1	2	3	4	5	6	7	8	9	10	
Lings et al.(185)	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	Moderate
Schultheis et al.(140)	Y	S	Y	Y	Y	Y	Y	Y	Y	Y	Moderate
Lincoln and Radford(141)	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	Moderate
Schultheis et al.(137)	Y	S	Y	Y	Y	N	Y	Y	NR	Y	Moderate

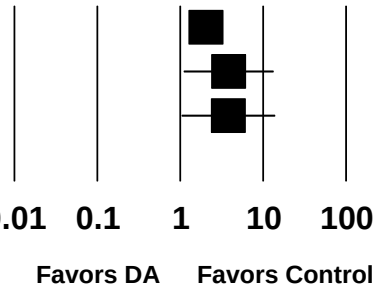
N = No
NR = Not reported
S = Somewhat representative or partially validated
Y = Yes

Appendix H: Sensitivity Analyses

Key Question 2

Figure 19. Removal of Each Individual Study Separately from Meta-analysis of Risk of Somnolence in Studies Using Dopamine Agonists

Study name	Statistics with study removed			
	Point	Lower limit	Upper limit	p-Value
Adler	2.045	1.300	3.217	0.002
Parkinson	3.836	1.090	13.498	0.036
Shannon	3.814	1.031	14.114	0.045



Appendix I: Unified Parkinson Disease Rating Scale (UPDRS) and Other Scales for Rating Parkinson's Disease

UPDRS

The UPDRS is a rating tool to follow the longitudinal course of PD. It is made up of the 1) mentation, behavior, and mood, 2) activities of daily living, 3) motor, and 4) complications of therapy sections. These are evaluated by interview. Some sections require multiple grades assigned to each extremity. A total of 199 points are possible. 199 represents the worst (total) disability), 0 = no disability. Section 4 (complications of therapy) is primarily used in patients receiving adjunct therapy.

I. Mentation, Behavior, Mood

Intellectual Impairment

0 - none
1 - mild (consistent forgetfulness with partial recollection of events with no other difficulties)
2 - moderate memory loss with disorientation and moderate difficulty handling complex problems
3 - severe memory loss with disorientation to time and often place, severe impairment with problems
4 - severe memory loss with orientation only to person, unable to make judgments or solve problems

Thought Disorder

0 - none
1 - vivid dreaming
2 - "benign" hallucination with insight retained
3 - occasional to frequent hallucination or delusions without insight, could interfere with daily activities
4 - persistent hallucination, delusions, or florid psychosis.

Depression

0 - not present
1 - periods of sadness or guilt greater than normal, never sustained for more than a few days or a week
2 - sustained depression for >1 week
3 - vegetative symptoms (insomnia, anorexia, abulia, weight loss)
4 - vegetative symptoms with suicidality

Motivation/Initiative

0 - normal
1 - less of assertive, more passive
2 - loss of initiative or disinterest in elective activities
3 - loss of initiative or disinterest in day to say (routine) activities
4 - withdrawn, complete loss of motivation

II. Activities of Daily Living

Speech

0 - normal
1 - mildly affected, no difficulty being understood
2 - moderately affected, may be asked to repeat
3 - severely affected, frequently asked to repeat
4 - unintelligible most of time

Salivation

0 - normal
1 - slight but noticeable increase, may have nighttime drooling
2 - moderately excessive saliva, hay minimal drooling
3 - marked drooling

Swallowing

0 - normal
1 - rare choking
2 - occasional choking
3 - requires soft food
4 - requires NG tube or G-tube

Handwriting

0 - normal
1 - slightly small or slow
2 - all words small but legible
3 - affected, not all words legible
4 - majority illegible

Cutting Food/Handing Utensils

0 - normal
1 - somewhat slow and clumsy but no help needed
2 - can cut most foods, some help needed
3 - food must be cut, but can feed self
4 - needs to be fed

Dressing

1 - somewhat slow, no help needed
2 - occasional help with buttons or arms in sleeves
3 - considerable help required but can do something alone
4 - helpless

Hygiene

0 - normal
1 - somewhat slow but no help needed
2 - needs help with shower or bath or very slow in hygienic care
3 - requires assistance for washing, brushing teeth, going to bathroom
4 - helpless

Turning in Bed/ Adjusting Bed Clothes

0 - normal
1 - somewhat slow no help needed
2 - can turn alone or adjust sheets but with great difficulty
3 - san initiate but not turn or adjust alone
4 - helpless

Falling-Unrelated to Freezing

0 - none
1 - rare falls
2 - occasional, less than one per day
3 - average of once per day
4 - >1 per day

Freezing When Walking

0 - normal
1 - rare, may have start hesitation
2 - occasional falls from freezing
3 - frequent freezing, occasional falls
4 - frequent falls from freezing

Walking

0 - normal
1 - mild difficulty, day drag legs or decrease arm swing
2 - moderate difficultly requires no assist
3 - severe disturbance requires assistance
4 - cannot walk at all even with assist

Tremor

0 - absent
1 - slight and infrequent, not bothersome to patient
2 - moderate, bothersome to patient
3 - severe, interfere with many activities
4 - marked, interferes with many activities

Sensory Complaints Related to Parkinsonism

0 - none
1 - occasionally has numbness, tingling, and mild aching
2 - frequent, but not distressing
3 - frequent painful sensation
4 - excruciating pain

III. Motor Exam

Speech

0 - normal
1 - slight loss of expression, diction, volume
2 - monotone, slurred but understandable, mod. impaired
3 - marked impairment, difficult to understand
4 - unintelligible

Facial Expression

0 - Normal
1 - slight hypomymia, could be poker face
2 - slight but definite abnormal diminution in expression
3 - mod. hypomimia, lips parted some of time
4 - masked or fixed face, lips parted 1/4 of inch or more with complete loss of expression

***Tremor at Rest**

Face

0 - absent
1 - slight and infrequent
2 - mild and present most of time
3 - moderate and present most of time
4 - marked and present most of time

Right Upper Extremity (RUE)

0 - absent
1 - slight and infrequent
2 - mild and present most of time
3 - moderate and present most of time
4 - marked and present most of time

LUE

0 -absent
1 -slight and infrequent
2 -mild and present most of time
3 -moderate and present most of time
4 -marked and present most of time

RLE

0 - absent
1 - slight and infrequent
2 - mild and present most of time
3 - moderate and present most of time
4 - marked and present most of time

LLE

0 - absent
1 - slight and infrequent
2 - mild and present most of time
3 - moderate and present most of time
4 - marked and present most of time

***Action or Postural Tremor**

RUE

0 - absent
1 - slight, present with action
2 - moderate, present with action
3 - moderate present with action and posture holding
4 - marked, interferes with feeding

LUE

0 - absent
1 - slight, present with action
2 - moderate, present with action
3 - moderate present with action and posture holding
4 - marked, interferes with feeding

***Rigidity**

Neck

0 - absent
1 - slight or only with activation
2 - mild/moderate
3 - marked, full range of motion
4 - severe

RUE

0 - absent
1 - slight or only with activation
2 - mild/moderate
3 - marked, full range of motion
4 - severe

LUE

0 - absent
1 - slight or only with activation
2 - mild/moderate
3 - marked, full range of motion
4 - severe

RLE

0 - absent
1 - slight or only with activation
2 - mild/moderate
3 - marked, full range of motion
4 - severe

LLE

0 - absent
1 - slight or only with activation
2 - mild/moderate
3 - marked, full range of motion
4 - severe

***Finger taps**

Right

0 - normal
1 - mild slowing, and/or reduction in amp.
2 - moderate impaired. Definite and early fatiguing, may have occasional arrests
3 - severely impaired. Frequent hesitations and arrests.
4 - can barely perform

Left

0 - normal
1 - mild slowing, and/or reduction in amp.
2 - moderate impaired. Definite and early fatiguing, may have occasional arrests
3 - severely impaired. Frequent hesitations and arrests.
4 - can barely perform

***Hand Movements (open and close hands in rapid succession)**

Right

0 - normal
1 - mild slowing, and/or reduction in amp.
2 - moderate impaired. Definite and early fatiguing, may have occasional arrests
3 - severely impaired. Frequent hesitations and arrests.
4 - can barely perform

Left

0 - normal
1 - mild slowing, and/or reduction in amp.
2 - moderate impaired. Definite and early fatiguing, may have occasional arrests
3 - severely impaired. Frequent hesitations and arrests.
4 - can barely perform

***Rapid Alternating Movements (pronate and supinate hands)**

Right

0 - normal
1 - mild slowing, and/or reduction in amp.
2 - moderate impaired. Definite and early fatiguing, may have occasional arrests
3 - severely impaired. Frequent hesitations and arrests.
4 - can barely perform

Left

0 - normal
1 - mild slowing, and/or reduction in amp.
2 - moderate impaired. Definite and early fatiguing, may have occasional arrests
3 - severely impaired. Frequent hesitations and arrests.
4 - can barely perform

***Leg Agility (tap heel on ground, amp should be three inches)**

Right

0 - normal
1 - mild slowing, and/or reduction in amp.
2 - moderate impaired. Definite and early fatiguing, may have occasional arrests
3 - severely impaired. Frequent hesitations and arrests.
4 - can barely perform

Left

0 - normal
1 - mild slowing, and/or reduction in amp.
2 - moderate impaired. Definite and early fatiguing, may have occasional arrests
3 - severely impaired. Frequent hesitations and arrests.
4 - can barely perform

***Arising From Chair (patient arises with arms folded across chest)**

0 - normal
1 - slow, may need more than one attempt
2 - pushes self up from arms or seat
3 - tends to fall back, may need multiple tries but can arise without assistance
4 - unable to arise without help

***Posture**

0 - normal erect
1 - slightly stooped, could be normal for older person
2 - definitely abnormal, mod. stooped, may lean to one side
3 - severely stooped with kyphosis
4 - marked flexion with extreme abnormality of posture

***Gait**

0 - normal
1 - walks slowly, may shuffle with short steps, no festination or propulsion
2 - walks with difficulty, little or no assistance, some festination, short steps or propulsion
3 - severe disturbance, frequent assistance
4 - cannot walk

***Postural Stability (retropulsion test)**

0 - normal
1 - recovers unaided
2 - would fall if not caught
3 - falls spontaneously
4 - unable to stand

***Body Bradykinesia/Hypokinesia**

0 - none
1 - minimal slowness, could be normal, deliberate character
2 - mild slowness and poverty of movement, definitely abnormal, or dec. amp. of movement
3 - moderate slowness, poverty, or small amplitude
4 - marked slowness, poverty, or amplitude

IV. Complications of Therapy (in the past week)

Dyskinesias

(Historical information.)
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

Duration: What proportion of the waking day are dyskinesias present?
(Historical information; may be modified by office examination.)
0 = Not disabling.
1 = Mildly disabling.
2 = Moderately disabling.
3 = Severely disabling.
4 = Completely disabled.

Disability: How disabling are the dyskinesias?
0 = No painful dyskinesias.
1 = Slight.
2 = Moderate.
3 = Severe.
4 = Marked.

Painful Dyskinesias: How painful are the dyskinesias?
(Historical information.)
0 = No
1 = Yes

Presence of Early Morning Dystonia

Clinical Fluctuations
0 = No
1 = Yes

Are "off" periods predictable?
0 = No
1 = Yes

Are "off" periods unpredictable?
0 = No
1 = Yes

Do "off" periods come on suddenly, within a few seconds?
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

What proportion of the waking day is the patient "off" on average?

Other Complications
0 = No
1 = Yes

Does the patient have anorexia, nausea, or vomiting?
0 = No
1 = Yes

Any sleep disturbances, such as insomnia or hypersomnolence?
(Record the patient's blood pressure, height and weight on the scoring form)
0 = No
1 = Yes

Does the patient have symptomatic orthostasis?

Modified Hoehn and Yahr Staging

Stage 0 = No signs of disease.
Stage 1 = Unilateral disease.
Stage 1.5 = Unilateral plus axial involvement.
Stage 2 = Bilateral disease, without impairment of balance.
Stage 2.5 = Mild bilateral disease, with recovery on pull test.
Stage 3 = Mild to moderate bilateral disease; some postural instability; physically independent.
Stage 4 = Severe disability; still able to walk or stand unassisted.
Stage 5 = Wheelchair bound or bedridden unless aided.

Schwab and England Activities of Daily Living Scale

100% = Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.
90% = Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.
80% = Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.
70% = Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.
60% = Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.
50% = More dependent. Help with half, slower, etc. Difficulty with everything.
40% = Very dependent. Can assist with all chores, but few alone.
30% = With effort, now and then does a few chores alone or begins alone. Much help needed.
20% = Nothing alone. Can be a slight help with some chores. Severe invalid.
10% = Totally dependent, helpless. Complete invalid.
0% = Vegetative functions such as swallowing, bladder and bowel functions are not functioning.