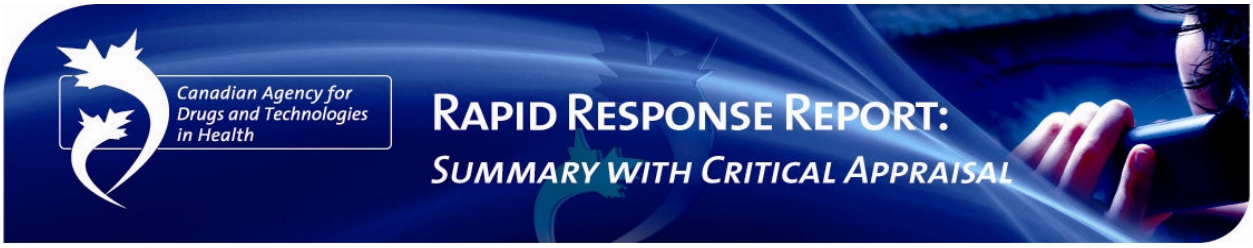

TITLE: Modafinil for Sleep Disorders and Fatigue Secondary to Multiple Sclerosis: A Review of the Clinical Efficacy and Safety

DATE: 27 July 2012

CONTEXT AND POLICY ISSUES

Modafinil is a central nervous system stimulant approved in Canada for the symptomatic treatment of excessive sleepiness in adult patients with narcolepsy, obstructive sleep apnea, and shift work sleep disorder.[1] Its efficacy has also tested in a number of off-label conditions such as fatigue related to multiple sclerosis (MS) or Parkinson's disease, cocaine addiction, attention deficit disorder, and depression.[2,3] Modafinil's mechanism of action of promoting wakefulness is not known, but it has a different pharmacologic profile than other stimulants used in sleep disorders, namely methylphenidate or amphetamines.[1]

This report will review the safety and efficacy of modafinil in patients with sleep disorders, or fatigue due to MS, in order to inform funding decisions.

RESEARCH QUESTIONS

1. What is the comparative clinical efficacy of modafinil compared with amphetamines, methylphenidate, or placebo for the treatment of sleep disorders?

2. What is the clinical evidence of the safety of modafinil compared with amphetamines, methylphenidate or placebo for the treatment of sleep disorders?

3. What is the comparative clinical efficacy of modafinil compared with amphetamines, methylphenidate or placebo for the treatment of fatigue secondary to multiple sclerosis?

4. What is the clinical evidence of the safety of modafinil compared with amphetamines, methylphenidate or placebo for the treatment of fatigue secondary to multiple sclerosis?

KEY MESSAGE

No conclusions can be drawn on the efficacy of modafinil compared to methylphenidate or amphetamines due to the absence of head-to-head clinical trials. Relative to placebo, modafinil was associated with improvements in sleepiness and some domains of health related quality of life, in patients with narcolepsy however, the clinical importance of these findings are unclear. No clear benefit was found with modafinil in patients with fatigue related to MS. The data available were insufficient to draw conclusions on the safety of modafinil in patients with sleep disorders or MS.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, EMBASE via OVID, The Cochrane Library (2012, Issue 6), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses and randomized controlled trials. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between Jan 1, 2007 and Jun 28, 2012.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to the selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with sleep related disorders or multiple sclerosis (MS)
Intervention	Modafinil
Comparator	Amphetamines, methylphenidate, placebo
Outcomes	Clinical benefit (e.g. management of sleep disorder, reduced sleepiness, reduced fatigue) Safety
Study Designs	Health technology assessment (HTA), systematic review, meta-analysis, randomized controlled trial (RCT)

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications, or were published prior to 2007. Because multiple systematic reviews were found with the same included studies, one methodologically robust review was selected for summary.

Critical Appraisal of Individual Studies

The methodological quality of systematic reviews was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.[4] Randomized controlled trials (RCTs) were assessed to determine if allocation to treatment groups was concealed from participants. Randomization, blinding, follow up, and intention to treat (ITT) analysis of data was also assessed.

SUMMARY OF EVIDENCE

The literature search yielded 202 citations. One additional report was identified by searching the grey literature. After screening of abstracts, sixteen potentially relevant studies were selected for full text review. Eight of the sixteen reports met the inclusion criteria.[2,5-11] Of these, three systematic reviews assessed treatments for fatigue in patients with MS.[9-11] There was an overlap in the RCTs included in these reports so only the Cochrane review,[9] which provided more complete information on the review methods and study results, was included in this report. The study selection process is outlined in a flowchart (Appendix 1).

Quantity of Research Available

Two systematic reviews,[2,9] and four RCTs[5-8] met the inclusion criteria.

No studies were found that compared modafinil to methylphenidate or amphetamines.

Summary of Study Characteristics

The characteristics of the included studies are summarized in Appendix 2.

Sleep Disorders

One systematic review (nine studies) and one additional RCT were identified, giving a total of ten RCTs which evaluated the efficacy of modafinil compared to placebo in patients with narcolepsy.[2,5] All studies were double blind, and six used a cross-over design. The sample size of the studies ranged from 10 to 283 patients and the average age per study ranged from 38 to 53 years. The dose of modafinil varied from 200 mg to 600 mg per day, and treatment was administered for 2 to 9 weeks. In the crossover studies, the washout period between treatments was one or two weeks in five studies; one study had no washout period.[2,5]

One RCT in patients with sleep apnea (N=21),[6] and one in patients with shift work sleep disorder (N=278)[7] met the inclusion criteria. In these double blind studies, patients were randomized to modafinil 200 mg/day,[7] 300 mg/day,[6,7] or placebo.[6,7] The treatment duration was three[6] or 12 weeks.[7] Patients with shift work disorder were younger (mean age 40 years) than those in the sleep apnea study (mean age 53 years).

Multiple Sclerosis

In the MS population, two double blind RCTs were included in the systematic review by Peuckmann-Post et al.[9] Both studies compared modafinil (100 mg to 400 mg per day) to placebo. Treatment duration was five or eight weeks. One RCT included 21 patients, who were a subgroup of a larger trial. The second study enrolled a total of 115 patients.[9] A third RCT was

found in the literature search.[8] This double blind RCT compared eight weeks of treatment with modafinil (100mg to 200 mg/day) to placebo. A total of 121 patients were enrolled with a mean age of 41 years.[8]

Summary of Critical Appraisal

The strengths and limitations of the included studies have been summarized in Appendix 3.

The authors of the two systematic reviews conducted comprehensive literature searches, screened studies based on defined inclusion and exclusion criteria, and incorporated the scientific quality of the included studies appropriately when formulating conclusions.[2,9] In one review,[9] the authors failed to report if study selection was done independently in duplicate, and data extraction was not verified for all reports.

The authors of the systematic reviews noted several limitations in the included studies: unclear allocation concealment (6 of 11 RCTs), incomplete information on randomization methods (5 RCTs), incomplete description of patients who withdrew (4 RCTs).[2,9] Of the other four double blind RCTs summarized in this report, three failed to report the methods to conceal the treatment allocation from participants.[5-7] Randomization[5-7] and blinding methods[7,8] were also not reported in detail in some studies. In one RCT,[7] 32% of patients did not complete the study.

Summary of Findings

The studies used a number of different sleepiness/fatigue, functioning and health related quality of life (HRQL) scales to measure the treatment effect of modafinil. A brief description of these scales has been provided in Appendix 6.

Efficacy

A summary of the efficacy results are listed in Appendix 4.

Sleep Disorders

In the systematic review of modafinil in patients with narcolepsy, the efficacy data were suitable for meta-analysis (Appendix 4 Table 1).[2] Modafinil reduced the number and the duration of severe somnolence, sleep attacks or naps per day. The duration of sleep attacks was 16 minutes shorter per day for modafinil versus placebo (95 % confidence interval (CI) -31 to -2 minutes). Objective measures of sleep latency [Multiple Sleep Latency Test (MSLT)] and wakefulness [Maintenance of Wakefulness Test (MWT)], and subjective measure of daytime sleepiness [Epworth Sleepiness Scale (ESS)] all showed statistically significant differences favoring modafinil versus placebo. The mean difference between modafinil and placebo was 1.1 minutes, 2.8 minutes, and -2.7 points in the MSLT, MWT, and ESS respectively. No between group differences were detected in the number of cataplexy attacks.

In one other cross-over RCT,[5] 15 narcolepsy patients reported statistically significantly less daytime sleepiness while taking modafinil than placebo. At the end of the three week treatment, the mean ESS score was 15.4 points while on placebo, and 10.2 points while on modafinil (ESS scores less than 10 are considered normal daytime sleepiness).[5]

In the RCT in patients with sleep apnea,[6] both the modafinil and placebo groups reported a statistically significant improvement in subjective daytime sleepiness, and the physical functioning domain of the SF-36. The between group differences, however, were less than 2 points on fatigue scales and were not statistically significant. The authors noted that there was a strong placebo effect observed among these patients with sleep apnea who were regular continuous positive airway pressure (CPAP) users.[6]

In one RCT, patients with shift work sleep disorder who received modafinil reported improvements in functioning as measured by the Function Outcomes of Sleep Questionnaire (FOSQ), and improvement in the emotional component of HRQL, but no change in sleep parameters or caffeine use.[7] Patients in the modafinil 300 mg/day and 200 mg/day groups scored 0.7 points higher ($P < 0.05$), and 0.4 points higher (P-value not significant), than those who received placebo on the FOSQ (maximum score 20 points). Modafinil treated patients showed a statistically significant improvement in the mental health composite score of the SF-36 relative to placebo (change from baseline 3.2, 3.7, and 0.7 in modafinil 300 mg, 200 mg and placebo groups, respectively). It should be noted that 32% of patients withdrew from the study before 12 weeks.[7]

Multiple Sclerosis

In patients with MS, pooled data from two RCTs,[9] and fatigue scores using the ESS and Fatigue Severity Scale (FSS) in a third trial,[8] showed no clinically important differences between modafinil and placebo (Appendix 4 Table 1). Health related quality of life scores were similar in the modafinil and placebo groups at the end of treatment ($P = 0.31$).

Safety

A summary of the safety data is provided in Appendix 5. Three reports in patients with sleep disorders,[2,6,7] and one in MS patients,[8] reported data on adverse events.

More patients who received modafinil withdrew from RCTs due to adverse events compared to those who received placebo.[2,6,7] The adverse event withdrawal rate ranged from 4% to 20% in the modafinil groups and 0% to 4% in the placebo groups.[2,6,7] In the systematic review of modafinil for narcolepsy, data were pooled for six RCTs and found a non-significant increased risk of withdrawals due to adverse events for modafinil versus placebo [relative risk (RR) 2.1, 95% CI 0.8 to 5.1].[2]

One serious adverse event (abnormal liver function test) was reported in a patient who received modafinil 300 mg per day.[7]

The most common adverse events reported included headache, nausea, diarrhea, nervousness, and flu like syndrome.

Limitations

Most of the RCTs evaluating the clinical effectiveness of modafinil had methodological limitations that could potentially bias the findings. Reporting of allocation concealment and randomization methods were not clear in nine and eight studies, respectively. These two elements are important to ensure there is no selection bias or imbalance of prognostic factors when patients are assigned to the treatments. Eight of the 15 RCTs enrolled ≤25 patients per

treatment group, and it is possible that despite randomization, prognostic factors were not evenly distributed between groups. One study may have been biased due to a withdrawal rate >20%, and patients in the modafinil 300 mg/day group were more likely to withdraw due to adverse events.

All but one cross-over study included a washout period between treatments. It is not known if there was any carry over effect from the first treatment into the second treatment period, or if patient blinding was maintained throughout the cross-over studies.

The included studies assessed short term efficacy only, as half the studies treated patients for 5 weeks or less (maximum study duration was 12 weeks). Some studies detected statistically significant differences between modafinil and placebo however, the clinical importance of these findings is not clear.

No studies compared modafinil to amphetamines or methylphenidate.

Data on adverse events was available in four of the 15 studies and was poorly reported. These studies lacked statistical power to detect less common adverse events associated with modafinil.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

A total of 15 double blind RCTs were found that evaluated the efficacy of modafinil in patients with narcolepsy (10 studies), sleep apnea (1), shift work sleep disorder (1), and fatigue due to MS (3). All studies compared modafinil to placebo, and none included methylphenidate or amphetamines as a comparator.

In patients with narcolepsy, modafinil was associated with statistically significant improvement in objective and subjective measures of sleepiness compared to placebo, as well as some domains of health related quality of life. The clinical importance of the between group differences reported is unclear.

No clear benefit was found with modafinil in patients with fatigue related to MS.

The data available were insufficient to draw conclusions on the safety of modafinil in patients with sleep disorders and MS. More patients treated with modafinil withdrew from the studies due to adverse events than those who received placebo. The most common adverse events reported included headache, nervousness, nausea, and diarrhea.

Most of the RCTs had methodological limitations that may have affected the findings. These limitations included unclear allocation concealment, limited sample size (median 63 patients), and incomplete reporting of randomization methods.

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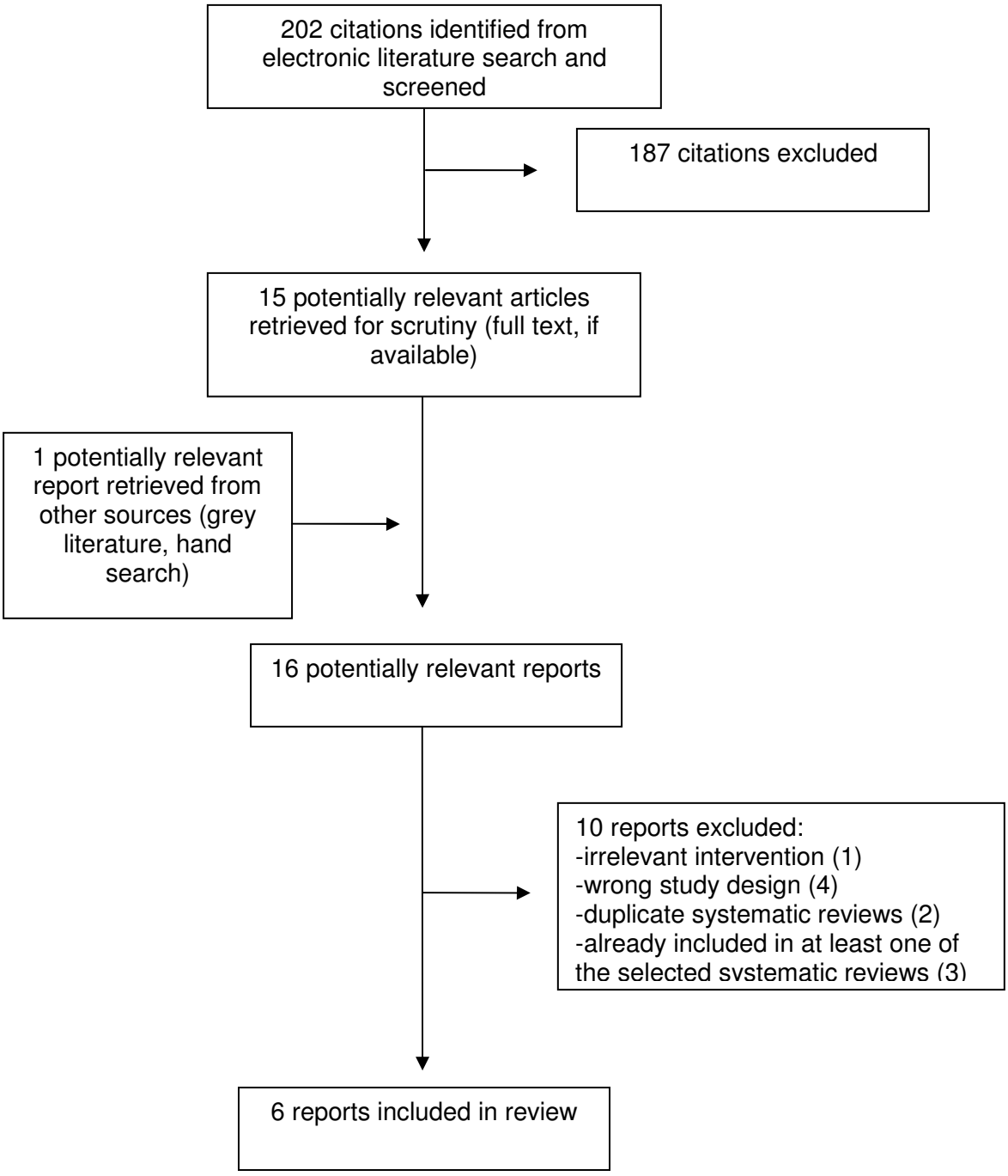
APPENDIX 1: Selection of Included Studies



Appendix 2: Study Characteristics

First Author, Publication Year, Country	Study Design	Population Characteristics, Number of studies/ participants, age, sex	Intervention, Comparator, Treatment duration	Key Outcomes
Sleep Disorders				
Narcolepsy				
Golicki 2010[2] Poland	SR	Narcolepsy (adults) N=9 RCTs Mean age: 39 to 53 years Male: 33% to 66%	Modafinil (any dose) Placebo or other active treatments	Fatigue, sleep attack frequency, cataplexy, HRQL, AE
Saletu 2009[5] Austria	RCT DB Crossover	Narcolepsy N=15 Withdrawals: 0 Mean age: 38 years Male: 47%	Modafinil 200 mg titrated to 400 mg per day (divided dose) Placebo Duration: 3 weeks per treatment with 1 week washout period in between	Fatigue (ESS, MWT)
Sleep Apnea				
Bittencourt 2008[6] Brazil	RCT DB	OSAS (aged 18 to 65 years) N=22 Withdrawals: 9% Mean age: 53 years Male: 85%	Modafinil 200 mg at 8 am + 100 mg at noon Placebo Duration: 3 weeks All patients received CPAP therapy and underwent a 7 day blinded placebo run in period.	Fatigue (ESS, MWT), HRQL, AE
Shift Work Sleep Disorder				
Erman 2007[7] US	RCT DB	Chronic SWSD (aged 18 to 60 years) N=278 Withdrawals: 32% Mean age: 40 years Male: 48%	Modafinil 200 mg/day Modafinil 300 mg/day Placebo Administered before night shift Duration: 12 weeks	Functioning (FOSQ), HRQL, sleep, AE
Multiple Sclerosis				
Peuckmann-Post 2010[9] Germany	SR	MS (age ≥18 years) N=2 RCTs Mean age: NR Male: NR	Modafinil (any dose) Placebo or other active treatments	Fatigue

First Author, Publication Year, Country	Study Design	Population Characteristics, Number of studies/ participants, age, sex	Intervention, Comparator, Treatment duration	Key Outcomes
Moller 2011[8] Germany	RCT DB	MS (aged 18 to 65 years) N=121 Withdrawals: 9% Mean age: 41 years Male: 30%	Modafinil 100 mg to 200 mg/day Placebo Duration: 8 weeks	Fatigue (FSS, other scales), HRQL, AE

AE=adverse events; DB=double blind; CPAP=continuous positive airway pressure; ESS=Epworth Sleepiness Scale; FSS=Fatigue Severity Score; HRQL=health related quality of life; MWT=Maintenance of wakefulness test; OSAS=obstructive sleep apnea syndrome; RCT=randomized controlled trial; SWSD=shift work sleep disorder

Appendix 3: Validity Assessment of Included Studies

First Author, Publication Year, Study Design	Strengths	Limitations
Sleep Disorders		
Golicki 2010[2] SR	- defined inclusion and exclusion criteria - comprehensive literature search including hand search and grey literature (all languages) - robust methods used for selection of studies, data extraction, validity assessment and meta-analysis	- excluded studies not listed
Saletu 2009[5] RCT	- randomized, double blind	- allocation concealment and randomization methods not reported - included a 1 week washout period between treatments but the authors did not assess if there was a carryover effect from first to second treatment - limited sample size (N=15)
Bittencourt 2008[6] RCT	- randomized, double blind	- no description of allocation concealment or randomization methods - limited sample size (N=22) - 18% withdrew from modafinil group; 0% placebo
Erman 2007[7] RCT	- randomized, double blind	- no description of allocation concealment, randomization or blinding methods - 32% withdrew from study
Multiple Sclerosis		
Peuckmann-Post 2010[9] SR	- defined inclusion and exclusion criteria - comprehensive literature search including hand search and grey literature - characteristics and risk of bias for included studies were reported	- unclear if study selection was done independently in duplicate - data extraction was verified for a subset of studies only
Moller 2011[8] RCT	- randomized, double blind, ITT analysis	- blinding methods not reported

ITT=Intention to treat: RCT=randomized controlled trial; SR=systematic review

Appendix 4: Efficacy

Table 1. Fatigue or Sleepiness Outcomes

Author, year, study design	Outcome	Treatment	Fatigue score		Between group difference, p value
			baseline	end of follow-up	
Sleep disorders					
Narcolepsy					
Golicki 2010[2] SR	Number of sleep attacks, naps/day	modafinil versus placebo	--	--	SMD (95% CI) -0.3 (-0.6 to -0.1)†
	Duration of sleep attacks, naps (min)		--	--	MD (95% CI) -16.4 (-31.2 to -1.7)†
	MSLT (min)		--	--	MD (95% CI) 1.1 (0.6 to 1.7)†
	MWT (min)		--	--	MD (95% CI) 2.8 (2.4 to 3.2)†
	ESS (points)		--	--	MD (95% CI) -2.7 (-3.4 to -2.1)†
	Number of cataplexy attacks/day		--	--	MD (95% CI) 0.02 (-0.3 to 0.3)
Saletu 2009[5] RCT	ESS (points)	modafinil	17.3**	10.2	P=0.004
		placebo		15.4	
	MWT (min)	modafinil	NR**	13.3	P=NS
		placebo		11.9	
Sleep apnea					
Bittencourt 2008[6] RCT	ESS (points)	modafinil	15.2	7.8	P=NS
		placebo	14.2	9.6	
	MWT (min)	modafinil	10.5	13.8	P=NS
		placebo	11.6	15.3	
Multiple sclerosis					
Peuckmann-Post 2010[9] SR	Fatigue score	modafinil	--	--	SMD (95% CI)* -0.14 (-0.48 to 0.21), p=NS
		placebo			
Moller 2011[8] RCT	FSS (points)	modafinil	6.0	5.3	P=0.07
		placebo	5.8	5.4	
	ESS (points)	modafinil	11.8	9.7	P=NS
		placebo	11.8	9.5	

CI=confidence interval; ESS=Epworth Sleepiness Scale; FSS=Fatigue Severity Score; MD=mean difference; min=minutes; MWT=Maintenance of wakefulness test; NS=not statistically significant; RCT=randomized controlled trial; SMD=standardized mean difference; SR=systematic review

*Meta-analysis of fatigue outcomes from two RCTs; negative numbers favor placebo, between group difference not statistically significant.

†Meta-analysis of fatigue related outcomes (2 to 6 RCTs pooled); statistically significant treatment effect favoring modafinil

**Cross-over study. ESS reported at the start of the study, but not prior to each treatment period. No data on MWT at baseline, or prior to each 3 week treatment.

Table 2: Functioning Outcomes

Author, year, study design	Treatment	N	Mean FOSQ change from baseline	Between group difference, p value versus placebo
Shift work sleep disorder				
Erman 2007[7] RCT	modafinil 300 mg	93	2.3	p<0.05
	modafinil 200 mg	92	2.0	P=NS
	placebo	93	1.6	

FOSQ=Function Outcomes of Sleep Questionnaire; NS=not statistically significant; RCT=randomized controlled trial

Table 3: HRQL and Other Outcomes

First Author, Publication Year, Study Design	HRQL	Other
Sleep disorders		
Narcolepsy		
Golicki 2010[2] SR	- HRQL was measured in 3 RCTs. Modafinil showed a statistically significant improvement in the mental health composite score of the SF-36 relative to placebo in 2 RCTs, and in 5 of 7 domains in 1 RCT that used a narcolepsy-specific HRQL instrument (details not reported).	--
Sleep apnea		
Bittencourt 2008[6] RCT	- Physician functioning domain (SF-36) was statistically significantly improved in both treatment groups (p=0.013, data not shown). - Between group differences were not reported.	--
Shift work sleep disorder		
Erman 2007[7] RCT	- Modafinil showed a statistically significant improvement in the mental health composite score of the SF-36 relative to placebo (change from baseline 3.2, 3.7, and 0.7 in modafinil 300 mg, 200 mg and placebo groups). - Physical component scores were not statistically significantly different between groups.	- Sleep parameters (time in bed, sleep duration, awakenings, time awake after sleep onset) and caffeine use were similar across treatment groups with no clinically meaningful changes observed.
Multiple sclerosis		
Moller 2011[8] RCT	-HRQL scores were similar in the modafinil and placebo groups at the end of treatment (p=0.31)	- As secondary outcomes, fatigue or sleepiness was measured using several different instruments, none of which were able to detect a statistically significant difference between treatment groups.

HRQL=health related quality of life; RCT=randomized controlled trial; SF-36=Short Form Health Survey 36; SR=systematic review

Appendix 5: Safety

First Author, Publication Year, Study Design	Treatment, daily dose	Withdrawals due to adverse events	Adverse events	Serious adverse events	Most common adverse events
Sleep disorders					
Golicki 2010[2] SR	Modafinil (200-600 mg)	RR (95% CI) 2.1 (0.8 to 5.1)*	NR	NR	headache, back pain, flu syndrome, nausea, diarrhea, dry mouth, nervousness, rhinitis
	placebo				
Bittencourt 2008[6] RCT	modafinil 300 mg	2 (18%)	14 events	NR	headache, irritability, gastric pain, anxiety
	placebo	0	5 events		
Erman 2007[7] RCT	modafinil 300 mg	19 (20%)	NR	1 (abnormal liver function test)	headache, nausea, nervousness, insomnia, accidental injury, hypertension, flu syndrome, anorexia
	modafinil 200 mg	5 (5%)		0	
	placebo	4 (4%)		0	
Multiple sclerosis					
Moller 2011[8] RCT	modafinil 100-200 mg	6 (treatment group NR)	NR	0	restlessness, nausea, diarrhea, gastric pain
	placebo			0	

CI=confidence interval; NR=not reported; RCT=randomized controlled trial; RR=relative risk; SR=systematic review
*Meta-analysis of six RCTs

Appendix 6: Description of Outcome Measurement Instruments

Epworth Sleepiness Scale (ESS)

The scale measures self-reported (subjective) daytime sleepiness.[3,6] Patients are asked to score their sleepiness in eight everyday situations requiring different levels of attention (e.g., watching TV, passenger in a car). Scale scores range from zero (would never doze) to three (high chance of dozing). A score of 0 to 10 is in the normal range, score 10 to 12 is borderline, and score 12 to 24 indicates excessive daytime sleepiness.[3]

Fatigue Severity Score (FSS)

The FSS is a nine item questionnaire that assessed the effect of fatigue on daily activities (prevention of physical function, interference with socioeconomic factors, motivational decrease). Each item is scored from one to seven with a total score ranging from 9 to 63.[8] Higher scores indicate more fatigue.

Multiple Sleep Latency Test (MSLT)

This test of daytime sleepiness is done in a sleep laboratory under standardized conditions. Patients undergo five nap trials and the time to sleep onset (sleep latency) is measured using EEG. An average time to fall asleep of less than five minutes indicates pathologic sleepiness. Normal subjects have average sleep latencies of 10 minutes or greater.[3]

Maintenance of Wakefulness Test (MWT)

This test measures the patient's ability to stay awake when seated in a dimly lit room and are told to stay awake. Patients are monitored using EEG and time to sleep onset is objectively measured. The average time of four nap tests is taken.[3]

Function Outcomes of Sleep Questionnaire (FOSQ)

This self-administered instrument measures the effect of excessive sleepiness on five domains of everyday living (vigilance, activity level, general productivity, social outcome, intimacy and sexual relationships). Patients are asked if they have difficulty performing each activity because of being sleepy or tired. Each domain is scored from one to four (no difficulty to extreme difficulty), with lower scores indicating greater functional impairment (total score 5 to 20).[7]

Short Form Health Survey 36 (SF-36)

This validated, self-administered HRQL instrument includes eight subscales that measure vitality, role physical, physical functioning, bodily pain, general health, social functioning, mental health and role emotional. The instrument also has two component summaries, the physical and mental component. The total score for all subscales and components is 0 to 100, with higher scores indicating better health.[7]