

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Czeisler CA, Walsh JK, Roth T, et al. Modafinil for excessive sleepiness associated with shift-work sleep disorder. *N Engl J Med* 2005;353:476-86.

1 **Supplementary Appendix**

2 **Introduction**

3 While night shift workers often experience sleepiness at night and insomnia,(6) a recent
4 study of 2,570 working adults between the ages of 18 and 65 years revealed that only 8
5 percent of night workers and 5.6 percent of rotating shift workers met both clinical
6 diagnostic criteria for SWSD.(7)

7 **Methods**

8 *Patients*

9 While some patients were recruited from within the investigators' clinical practices, most
10 patients were recruited through advertising campaigns conducted by investigators and/or
11 by a central agency (Dorland Sweeny Jones, Philadelphia, PA). Print and radio
12 advertisements developed by the central agency recruited individuals who had difficulty
13 staying awake when working night shifts and sleeping during the day. Interested
14 individuals were prescreened telephonically.

15

16 Main exclusion criteria were a diagnosis by history and/or diagnostic polysomnogram of
17 a concurrent sleep disorder other than chronic shift work sleep disorder; the presence of
18 clinically significant, uncontrolled psychiatric or medical conditions; abuse of alcohol,
19 narcotics, or other drugs, as defined by criteria provided in the *Diagnostic and Statistical*
20 *Manual of Mental Disorders, fourth edition text revision*(4); drug sensitivity to
21 stimulants; caffeine consumption averaging more than 600 mg per day within 1 week of
22 baseline; and use of protocol-prohibited prescription medications (e.g., any medication
23 that could make a patient feel sleepy, such as sedating antihistamines or selective

1 serotonin reuptake inhibitors; tricyclic antidepressants; lithium; antipsychotics;
2 anticoagulants; anticonvulsants; monoamine oxidase inhibitors; benzodiazepines; or
3 psychostimulants) or clinically significant use of over-the-counter drugs within 2 weeks
4 of baseline. Clinical laboratory testing was carried out by Central Reference Laboratory
5 (CRL) (Lenexa, KS) for all sites.

6

7 *Study Design*

8 The 3-month evaluation was required to occur at least 10 weeks after baseline.

9 Patients were evaluated individually under controlled laboratory conditions while being
10 continuously monitored by research staff. During the laboratory night shifts, light levels
11 were maintained at less than or equal to 50 lux, and time cues provided by television,
12 radio, cell phones, and clocks were prohibited. Exercise, napping, and smoking were
13 proscribed. Meals, sleep latency and performance testing, and free time were scheduled.
14 Patients were allowed to read, play games, listen to music, conduct hobbies, or converse
15 with research staff during free time.

16

17 Patients whose night shifts began after 2400 h were instructed to take study drug no later
18 than 2400 h. Patients working rotating shifts were instructed to take study drug before
19 scheduled night shifts but not before day or evening shifts. On the evening of laboratory
20 night shifts, study drug was taken at 2200 h with a light meal. As noted in the main text,
21 adults (18–60 yr) who worked each month at least 5 night shifts ≤ 12 hours, with ≥ 6 hours
22 worked between 2200 and 0800 h and with at least 3 shifts occurring consecutively, were
23 eligible. The night shift schedule had to be maintained for the duration of the study.

1

2 *Efficacy Measures*

3 For the Multiple Sleep Latency Test, patients were instructed to lie quietly in the dark and
4 attempt to sleep during four 20-minute sessions conducted at 2-hour intervals.

5 Polysomnographic data from all sites collected for Multiple Sleep Latency Testing were
6 scored centrally without knowledge of treatment group by the Sleep Medicine and
7 Research Center, Unity Health Services (Chesterfield, MO). Sleep latency was measured
8 as the elapsed time from the time of lights out to the first epoch scored as sleep. For a
9 scoring epoch of 30 seconds, this criterion was achieved when sleep occupied greater
10 than 50 percent of any 30 seconds. If a patient did not fall asleep during a specific nap,
11 sleep latency was set at 20 minutes. PVT data were evaluated without knowledge of
12 treatment group in the Unit for Experimental Psychiatry at the University of Pennsylvania
13 School of Medicine.

14

15 Electronic diaries were used to record maximum level of sleepiness; number of
16 unintentional sleep episodes; number of intentional sleep episodes; number of caffeinated
17 drinks; number of mistakes, near misses, or accidents on the night shift and level of
18 sleepiness, number of unintentional sleep episodes, and number of accidents or near
19 misses on the commute home. In the electronic diaries, patients also provided the time
20 spent in bed and sleep duration during the days following night shifts and recorded the
21 number of caffeinated drinks consumed from the end of the night shift until 60 minutes
22 after waking up from the last sleep episode. The PHT Corporation (Charlestown, MA)
23 managed electronic patient diary data centrally for all sites.

1

2 *Other Assessments*

3 For polysomnography, patients were scheduled to sleep in dark, sound-attenuated,
4 temperature-controlled rooms and were instructed to remain in bed even if they awakened
5 before the end of the scheduled sleep episode. The start time used for laboratory
6 polysomnography was consistent with the average habitual bedtime of 1030 h (standard
7 deviation, 170 min) reported by participants in the study. All polysomnographic
8 recordings were scored centrally without knowledge of treatment group by the Henry
9 Ford Hospital Sleep Disorders and Research Center (Detroit, MI).

10

11 The main variable for circadian phase assessment was melatonin midpoint, (50) which
12 was derived by adding 6 hours to the dim light melatonin onset and defined as the time
13 when salivary melatonin levels rose to and were sustained above 3 picograms per
14 milliliter in saliva. When calculation of melatonin onset was not possible, melatonin
15 midpoint was derived by subtracting 6 hours from dim light melatonin offset and defined
16 as the time when salivary melatonin levels decreased to 3 picograms per milliliter.

17 Melatonin assays were conducted by Bioanalytical Systems, Inc. (BAS Analytics, West
18 Lafayette, IN). Only the 99 patients in whom melatonin onset was measurable at baseline
19 and final visits, or in whom melatonin offset was measurable at both visits, were included
20 in the circadian phase analysis, which was conducted without knowledge of treatment
21 group.

22

23 *Safety Assessments*

1 Randomized patients receiving at least one dose of study medication were evaluated for
2 safety. Adverse events were recorded without knowledge of treatment group and then
3 analyzed by treatment group, severity (mild, moderate, or severe), seriousness, and
4 relationship to study medication. Interpretation of electrocardiograms at all sites was
5 done by Covance Central Diagnostics (Reno NV).

6

7 *Statistical Analysis*

8 Since there were no published data using the MSLT for patients with excessive sleepiness
9 associated with chronic shift work sleep disorder, the a priori power analysis was based
10 on data from patients with excessive sleepiness associated with narcolepsy and patients
11 with obstructive sleep apnea. Based on these data the standard deviation of the change
12 from baseline for the Multiple Sleep Latest test sleep latency was estimated at
13 4.0 minutes. Therefore, a sample size of 81 patients in each treatment group was
14 calculated to provide approximately 80% power to detect a treatment difference of
15 2 minutes.

16

17 Randomization was stratified by center, and within each center, it was stratified by those
18 patients who worked 5 to 10 night shifts per month and those patients who worked more
19 than 10 night shifts per month. The randomization was generated to enable the balanced
20 treatment assignments from each of 2 strata. Stratum was not included in the model
21 because very few patients (9.8%) were rotating night shift workers. No imputation was
22 performed to account for missing data. All analyses were performed on the observed data
23 only except for the final visit analysis, where last-observation-carried-forward

1 methodology was used (i.e., data from the patient’s last visit on or before month 3 was
2 used).

3

4 For Psychomotor Vigilance Task analyses, 29 patients at three study centers were
5 excluded because of equipment or procedural data collection problems.

6 For the MSLT, overall sleep latency was calculated by averaging the four tests between
7 0200 h and 0800 h. If a sleep latency value were missing, the overall latency was to be
8 calculated on the basis of the non-missing data. However, there were no data missing for
9 the MSLT at any time.

10

11 **Results**

12 *Patient Disposition and Characteristics*

13 Screened patients included those referred from the central advertising agency, patients
14 recruited from the investigator’s own advertising efforts, and investigators’ patients.

15

16 **Safety Outcomes**

17 Adverse events leading to discontinuation that were considered by the investigator to be
18 possibly related to 200-mg modafinil were insomnia (n=1), flatulence (n=1), abdominal
19 pain (n=1), and vasodilatation (n=1).

20

21 **Discussion**

22 In the present study, patients diagnosed with SWSD exhibited persistently high levels of
23 nighttime sleepiness and averaged nocturnal sleep latencies of 2 minutes at pretreatment

1 baseline, which is comparable to that observed during the daytime in untreated patients
2 with narcolepsy. At study initiation, one-half of patients were rated between markedly ill
3 and extremely ill on the Clinical Global Impression of Severity and patients averaged a
4 performance lapse every minute on the Psychomotor Vigilance Task. During the study
5 more than half of those in the placebo arm reported at least one accident or near miss at
6 work or on the commute home from work, which is consistent with a report that SWSD
7 patients have a higher rates of sleepiness-related accidents than night shift workers
8 without the disorder.(6) Reduction of sleepiness should thus be a primary goal in the
9 treatment of patients with SWSD.

10

11 There is therefore a need to identify the neurobiological factors that serve to predispose a
12 subset of shift workers to experience shift work sleep disorder. Candidate reasons for
13 profound levels of physiological sleepiness observed in this study include an inability to
14 make any circadian phase adjustment to the inverted sleep-wake schedule; the cumulative
15 effects of chronic partial sleep deprivation (26); and differential neurobiological
16 vulnerability to impairment from sleep loss(22) or circadian misalignment. Of course,
17 there could be behavioral causes for the manifestation of high levels of sleepiness, such
18 as working additional jobs that reduce time for sleep to very low levels. There was no
19 evidence that this was the case in the present study. Patients' average daily time in bed
20 for sleep reported in the electronic diaries on work days was between 6.7 hours and 7.1
21 hours per day, with no difference between those treated with 200-mg modafinil versus
22 placebo.

23

1 Other controlled studies that specifically address shift work type in patients with this
2 disorder are warranted. Since the participants were limited to patients who consumed less
3 than 600 mg of caffeine daily, our findings may only apply to this population. This study
4 evaluated the efficacy of modafinil in the subset of patients who met clinical criteria for
5 SWSD and provided objective evidence of excessive nighttime sleepiness and daytime
6 insomnia, and our findings may only apply to this population.

7
8 Interventions such as appropriately timed bright light and dark periods to facilitate
9 entrainment of the circadian cycle to work-rest schedules(34-38) have been shown to
10 improve alertness and cognitive performance during waking hours(34) and reverse
11 daytime insomnia,(39) although issues of practical application currently limit the
12 widespread use of bright light, and it has not been studied in patients with shift work
13 sleep disorder. Similarly, exogenous administration of melatonin, a pineal hormone with
14 circadian phase-shifting(40) and sleep-promoting(41) effects, requires further study, as
15 the efficacy of this agent has been variable across controlled clinical studies.(41-45) and
16 is untested in patients with shift work sleep disorder. Although shifting the circadian
17 pacemaker during the night shift may be a desirable course of therapy for patients
18 diagnosed with SWSD, interventions that improve daytime sleep efficiency or
19 wakefulness at night may be necessary when circadian phase shifting manipulations are
20 not feasible or when such efforts fail to fully resolve excessive sleepiness at work,
21 particularly for those in occupations with an elevated safety risk. Sedative-hypnotic
22 medications have been reported to increase daytime sleep in rotating shift
23 workers,(42,43) however, this may not improve alertness and performance during night

1 shifts(46) and the efficacy of hypnotics in shift work sleep disorder is unknown. Strategic
2 napping during the night shift has been shown to improve alertness,(47) although care
3 must be taken to avoid the adverse consequences of sleep inertia.(48) Many night shift
4 workers drink caffeinated beverages to promote arousal. The effectiveness of caffeine in
5 improving alertness has been demonstrated in a number of placebo-controlled studies
6 conducted in volunteers during simulated night shifts,(31,33) but it is untested in patients
7 with shift work sleep disorder. Some night shift workers use nicotine for this purpose,
8 notwithstanding its adverse health consequences.

9

10 **References**

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- 21
- 22

1

2 **Supplementary Appendix Table 1**

3 **Reasons Patients Were Screened but not Randomized and Patient Withdrawals**

4 **After the Start of Treatment by Month**

5 **Reason Patients Were Not Randomized**

6 Inclusion criteria violation (n=179)

7 Number of night shifts worked/month, number of hours worked/night shift, time
8 of night shift (n=22)

9 Complaint of excessive sleepiness in relation to night shifts (n=5)

10 Clinical Global Impression of Severity score of at least moderately ill (n=13)

11 Mean sleep latency of 6 minutes or less from a screening Multiple Sleep Latency
12 Test (n=53)

13 Less than 85% sleep efficiency (changed to 87.5%) determined from daytime
14 polysomnography (n=107)

15 Did not meet criteria for Chronic shift work sleep disorder (n=21)

16 Did not meet criteria for contraception usage (n=1)

17 Exclusion criteria violation (n=89)

18 Diagnosis of current sleep disorder (n=14)

19 Excessive caffeine consumption (n=2)

20 Used disallowed prescription or clinically significant use of OTC drugs (n=6)

21 Alcohol, narcotic, drug abuse (n=4)

22 Positive urine drug screen (n=19)

23 Clinically significant uncontrolled psychiatric condition (n=9)

- 1 Clinically significant uncontrolled medical condition (n=36)
- 2 Clinically significant deviation from normal in physical examination (n=20)
- 3 Seizure disorder either past or present (n=1)
- 4 Withdrawn consent (screening period) (n=69)
- 5 Lost to follow-up (screening period) (n=49)
- 6 Other (n=41)
- 7 (Patients could be counted more than once.)

8

9 **Patient Withdrawals After the Start of Treatment by Month (n=51)**

10 **Month 1 (n=7)**

- 11 Lost to follow up (total, n=4 [placebo, n=1; modafinil, n=3])
- 12 Noncompliance (total, n=1 [placebo, n=1])
- 13 Other (total, n=2 [modafinil, n=2])

14 **Month 2 (n=26)**

- 15 Adverse event (total, n=5 [placebo, n=3; modafinil, n=2])
- 16 Withdrawn consent (total, n=7 [placebo, n=5; modafinil, n=2])
- 17 Lost to follow up (total, n=5 [placebo, n=3; modafinil, n=2])
- 18 Noncompliance (total, n=2 [placebo, n=2])
- 19 Protocol violation (total, n=1 [placebo, n=1])
- 20 Other (total, n=6 [placebo, n=1; modafinil, n=5])

21 **Month 3 (n=18)**

- 22 Adverse event (total, n=2 [placebo, n=1; modafinil, n=1])

- 1 Withdrawn consent (total, n=4 [placebo, n=2; modafinil, n=2])
- 2 Lost to follow up (total, n=4 [placebo, n=3; modafinil, n=1])
- 3 Protocol violation (total, n=1 [modafinil, n=1])
- 4 Other (total, n=7 [placebo, n=4; modafinil, n=3])

1 **Supplementary Appendix Table 2**
 2 **Clinical Global Impression of Change At Final Visit**
 3

CGI-C rating	Number (%) of Patients	
	Placebo (n=104)	200-mg Modafinil (n=89)
Very much improved	8 (8)	21 (24)
Much improved	13 (13)	28 (31)
Minimally improved	16 (15)	17 (19)
No change	61 (59)	20 (22)
Minimally worse	4 (4)	2 (2)
Much worse	2 (2)	1 (1)
Very much worse	0 (0)	0 (0)
P-value		<0.001

1 **Supplementary Appendix Table 3.**
2 **Serious Adverse Events; Adverse Events Rated Severe; and Adverse Events Leading**
3 **to Discontinuation in Patients Diagnosed with Shift Work Sleep Disorder Treated**
4 **With Modafinil or Placebo.**

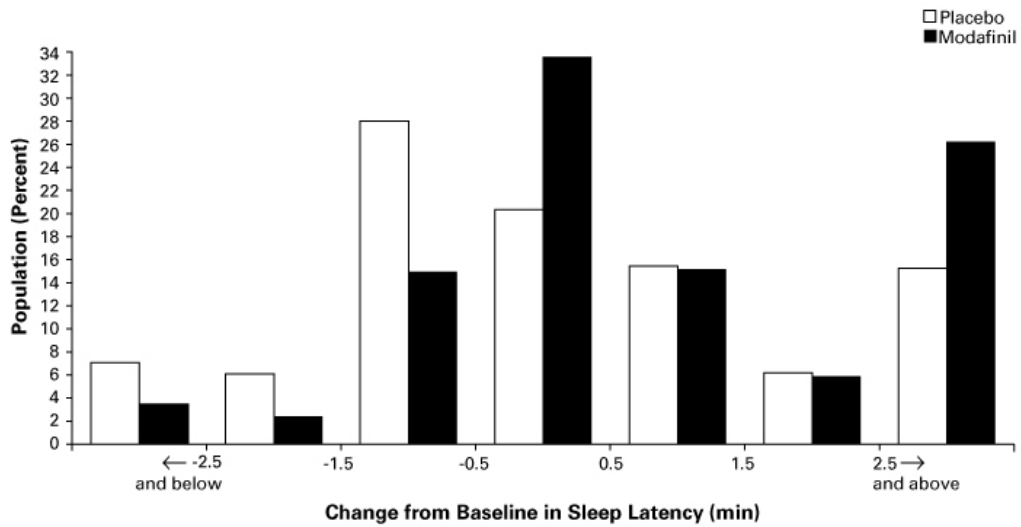
Adverse Event	Number (%) of Patients	
	Placebo (n=108)	200-mg Modafinil (n=96)
Serious adverse event*		
Accidental injury	1 (<1)	(0)
Adverse event rated severe†		
Migraine	2 (2)	(0)
Accidental injury	1 (<1)	1 (1)
Headache	1 (<1)	1 (1)
Chest pain	(0)	1 (1)
Electrocardiogram abnormality	(0)	1 (1)
Insomnia	(0)	1 (1)
Photophobia	(0)	1 (1)
Sinusitis	(0)	1 (1)
Tooth disorder	(0)	1 (1)
Dry mouth	1 (<1)	(0)
Influenza syndrome	1 (<1)	(0)
Nausea	1 (<1)	(0)
Adverse event leading to discontinuation‡		
Insomnia	0 (0)	2 (2)
Headache	2 (2)	0 (0)
Flatulence	0 (0)	1 (1)
Abdominal pain	0 (0)	1 (1)
Vasodilatation	0 (0)	1 (1)
Somnolence	1 (<1)	0 (0)
Dizziness	1 (<1)	0 (0)
Dyspepsia	1 (<1)	0 (0)
Kidney calculus	0 (0)	1 (1)
Tachycardia	1 (<1)	0 (0)

5 *Serious adverse events included untoward medical occurrences of all cause that were life
6 threatening; caused or prolonged in-patient hospitalization; resulted in persistent or
7 significant disability or incapacity, congenital anomaly/birth defect, or death; or required
8 medical or surgical intervention to prevent these outcomes.

1 † Adverse events that were not serious but resulted in the inability to carry out usual
2 activities were defined as severe. Such events were reported in 11 patients (6 and 5
3 patients in the modafinil and placebo groups, respectively).

4 ‡Adverse events for which a patient could be withdrawn included but were not limited to
5 intercurrent illness that could significantly affect response or assessment, severe side
6 effects, or development of hypersensitivity to study drug. Adverse events of all cause are
7 included in the table. Some patients experienced more than 1 adverse event leading to
8 discontinuation.

1 **Supplementary Appendix Figure 1**
2 **Population Distributions For Level of Change From Baseline in Sleep Latency For**
3 **Patients Diagnosed With Shift Work Sleep Disorder Treated with 200-mg Modafinil**
4 **(n=86) or Placebo (n=96) at the Final Visit**
5

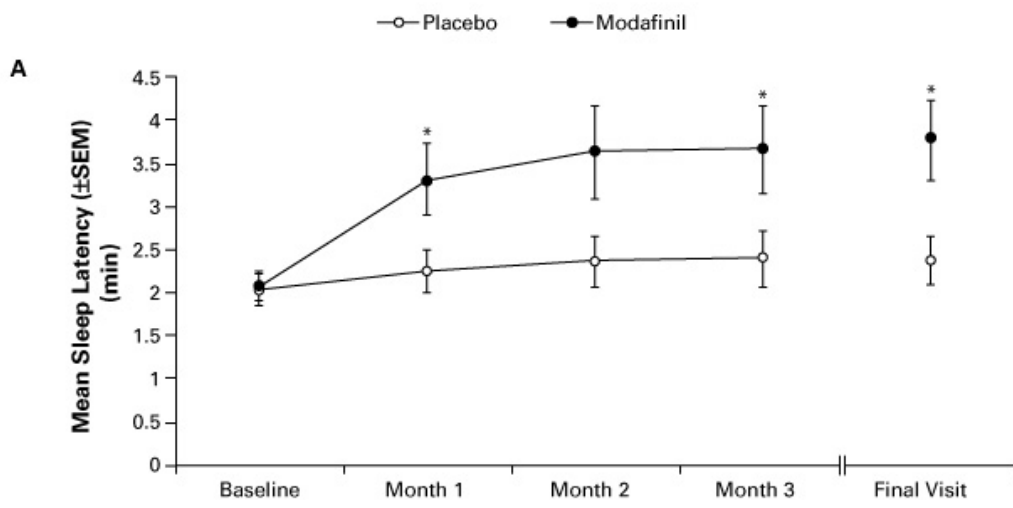


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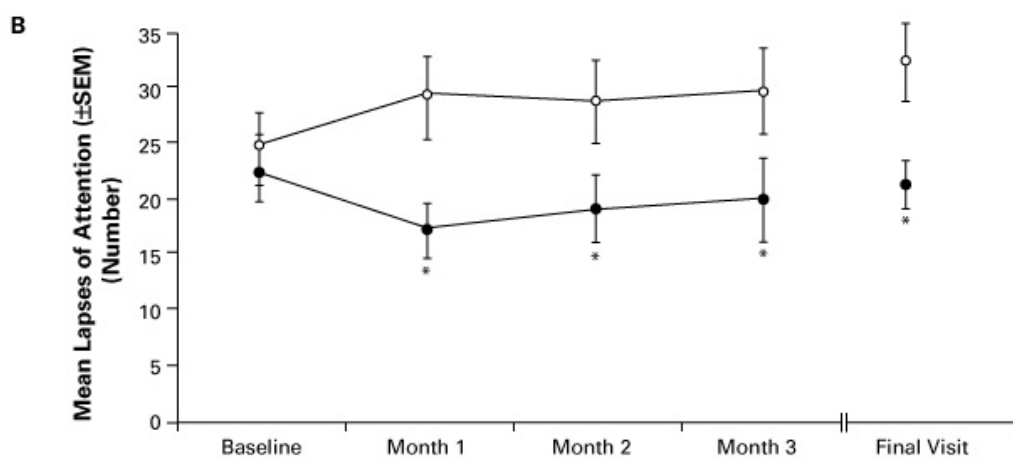
Supplementary Appendix Figure 2

Overall Mean Values for Sleep Latency (Panel A) from the Multiple Sleep Latency Test, Mean Lapses of Attention During Psychomotor Vigilance Task Performance (Panel B), and Patient-Estimated Sleepiness on the Karolinska Sleepiness Scale (Panel C) for Patients Diagnosed With Shift Work Sleep Disorder Treated With Placebo or 200-mg Modafinil at Baseline and the 1-Month, 2-Month, 3-Month, and Final Visit. Panel A: The difference in the change from baseline for modafinil versus placebo was statistically significant at Month 1 (asterisk, $P=0.01$), Month 3 (asterisk, $P=0.01$), and the final visit (cross, $P=0.002$). Panel B: The difference in the change from baseline for modafinil versus placebo was statistically significant at Month 1 (asterisk, $P<0.001$), Month 2 (cross, $P=0.004$), Month 3 (double cross, $P=0.01$), and the final visit (asterisk, $P<0.001$). Panel C: The difference in the change from baseline for modafinil versus placebo was statistically significant at Month 1, Month 2, Month 3, and the final visit (asterisk, $P<0.001$).

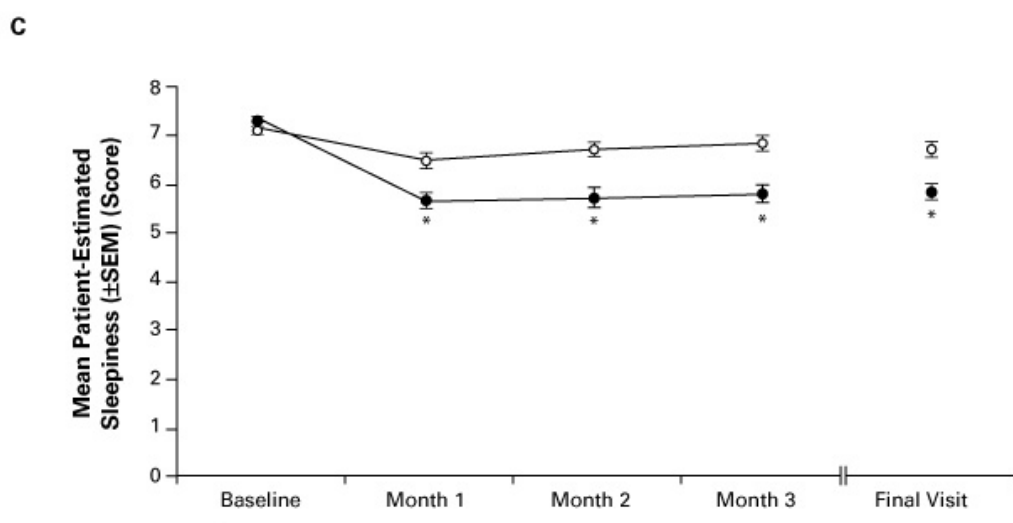
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*P<0.05 change from baseline versus placebo



*P<0.05 change from baseline versus placebo (Wilcoxon)



*P<0.001 change from baseline versus placebo