

**Kaiser PR, Valko PO, et al. Modafinil ameliorates excessive daytime sleepiness after traumatic brain injury. *Neurology* 2010;75:1780-85.**

Design: Randomized clinical trial

Population/sample size/setting:

- 20 (17 men, 3 women, mean age 40) with closed head injury resulting in mild to severe TBI in a university department of neurology in Zurich
- Inclusion criteria were fatigue or excessive daytime sleepiness (EDS) since TBI, assessed by the Fatigue Severity Scale (FSS) scores above 4.0 and Epworth Sleepiness Scale (ESS) scores above 10
- Exclusion criteria were other disorders that might cause sleep-wake disturbances
  - o This included neurologic or psychiatric diagnoses, medication use, and disturbances other than posttraumatic vigilance impairment
  - o Chronic sleep deprivation (patients with EDS who slept >2 hours more on weekends than during the week) were excluded

Main outcome measures:

- Baseline evaluation included the Beck Depression and Anxiety Inventory, wrist actigraphy for 2 weeks using the manufacturer's software algorithm for activity/rest cycles, and one conventional nocturnal sleep lab test
- Maintenance of wakefulness test (MWT) was administered after the sleep lab; this measures whether the participant can remain awake for 40 minutes when sitting quietly in a darkened room, and is done every 2 hours 4 times a day
- Randomized to treatment with modafinil (n=10) or placebo (n=10)
  - o Modafinil 100 mg capsules and identical appearing placebo were supplied by the manufacturer
  - o Starting dose was 1 capsule in the morning, which could be doubled to 2 capsules if efficacy was lacking and side effects had not appeared
- Treatment was continued for 6 weeks, after which EDS, FSS, actigraphy, sleep lab, and MWT measurements were repeated
  - o Primary stated outcomes were EDS, FSS, and MWT
- After 6 weeks, the two groups did not differ on the changes in FSS scores, but mean ESS scores decreased in the modafinil group (by 2.3 points) and increased in the placebo group (by 0.7 points)
  - o Excessive daytime sleepiness (ESS>10) was still present in 3 patients in each group at the end of 6 weeks
- The MWT increased by 8.4 minutes in the modafinil and by only 0.4 minutes in the placebo group
- Actigraphy in the modafinil group showed an increase of 1.9 hours per day awake, but decreased 0.3 hours in the placebo group; this was not statistically significant (p=0.33)
- Overall subjective estimation of patients on vigilance improvement was similar in the two groups; these estimations did not correlate with ESS, FSS, or MWT results

Authors' conclusions:

- Modafinil appeared effective in improving sleepiness but not fatigue; this may be because the two symptoms are distinct entities with different pathophysiology
- Higher doses than the 100-200 mg in this study might have greater benefits

Comments:

- Although most important sources of bias were controlled, the study is very small and should be seen as a pilot study suggesting that modafinil warrants more investigation
- Having only 10 patients per group makes multiple regression an unsuitable method for analyzing results, especially with five covariates
- The text reports that awake time by actigraphy improved by 1.9 hours in the modafinil group, but Table 1 reports this as 1.9%; the former is important, and the latter is trivial
- Multiple comparisons were done, but adjustment of p values for multiple comparisons are not reported

Assessment: Inadequate for evidence of effectiveness of modafinil (small pilot study which supports the value of further investigation)