

Jha A, Weintraub A, et al. A Randomized Trial of Modafinil for the Treatment of Fatigue and Excessive Daytime Sleepiness in Individuals with Chronic Traumatic Brain Injury. J Head Trauma Rehabil 2008;23(1):52-63.

Design: Crossover randomized clinical trial

Population/sample size/setting:

- 51 patients (35 men, 16 women, mean age 38) treated for excessive daytime sleepiness (EDS) following TBI at a specialized rehabilitation hospital in Denver
- Eligible patients were between ages 18 and 65, had received inpatient rehabilitation for TBI at the hospital conducting the study, and were at least one year post-injury
- Exclusion criteria were conditions (such as aphasia, dementia, substance abuse, non-English speaking) which would obscure the evaluation of the study outcome, conditions such as sleep apnea or narcolepsy which also cause EDS, concurrent medical conditions which may cause fatigue or diminished arousal, epilepsy, cardiovascular, renal, or hepatic disease, and pregnancy

Main outcome measures:

- Every patient received both modafinil and identical-appearing placebo during the study; the order in which the two treatments were taken was determined by randomization
- Treatment periods lasted 10 weeks, and were separated by 4 weeks during which no drug was taken
 - o Tablets supplied by the manufacturer contained 100 mg modafinil or placebo
 - o Dose titration was done with a starting dose of 100 mg for 3 days, then 200 mg for 11 days, then 400 mg for 8 weeks
 - o 27 patients took modafinil first, followed by placebo; 24 patients started on placebo and then took modafinil
- Three primary outcome were measured, two for fatigue and one for EDS
 - o Fatigue was measured with the Fatigue Severity Scale (FSS) and the Modified Fatigue Impact Scale (MFIS)
 - o EDS was measured with the Epworth Sleepiness Scale (ESS), where a score ≥ 10 defines EDS
 - o The primary analysis was the treatment effect after 4 weeks of treatment, adjusted for baseline and period effects
 - o Carryover effects were assessed by a regression model to determine if the effect of modafinil depended on whether it was taken before or after taking the placebo
- Secondary outcome measures included SF-12 and scales for post-concussion cognition, sustained visual attention, and depression
- From initial Glasgow Coma Scale scores, 26 patients had severe TBI, 12 had moderate, and 13 had mild TBI

- For the primary outcomes, both placebo and modafinil groups improved by the 4th week, but the improvements were statistically equal
 - o There was a transient advantage (1.2 points) of modafinil over placebo on the ESS when the 4 week ESS scores were adjusted for the baseline value and for period effects, but this difference was not present at 10 weeks
- There appeared to be no carryover effects from the first treatment period to the second
- Baseline depression and fatigue scores did not affect the response to treatment
- Insomnia was reported more often during modafinil treatment (n=10) than with placebo (n=2); other adverse effects were approximately equally distributed under different treatment conditions
- Blinding, judged by how well participants guessed whether they were taking modafinil or placebo, appeared successful; the correct guess rate was about 50% for both treatments

Authors' conclusions:

- Modafinil does not appear to be more effective than placebo for fatigue after TBI
- Modafinil may be effective for EDS in chronic TBI, but the benefits may be time-limited with benefits only for short-term use of modafinil
- Individual responses to modafinil were variable, and certain subgroups may benefit more than others; characteristics that identify patients likely to benefit need to be sought in future studies

Comments:

- Methodologically the study is of high quality, with good control of threats to internal validity and adequate reporting of both period and carryover effects in addition to treatment effects
- Headaches were a common adverse event, but are a common event in the TBI population; without more information about their frequency at baseline, it is not clear whether they increased in frequency or were attributable to treatment
- The treatment population was heterogeneous, with one half having severe TBI and one quarter having moderate and one quarter mild TBI
- If severity of TBI is one factor that affects response to modafinil, this would be one subgroup analysis to be sought in future studies
 - o It is biologically plausible that difficulties in wakefulness are different in patients who have been comatose than in patients who were not
 - o Some statistical interactions were reported, but no interaction term for severity of TBI was reported in the analyses
 - o Because the standard errors of interaction terms tend to be large, it is not likely that this term would have been "significant," but a separate reporting of the response rates would be of interest
- The study did have 90% power to detect a treatment effect of one-half standard deviation in the main outcome variable, but this applies to the entire

enrolled patient population, and not to the subgroups, if severity is a factor in response to modafinil

- For the 13 patients with mild TBI, there would be 90% power to detect a large effect (about 1 full standard deviation), but the power to detect a treatment effect of one-half standard deviation is only about 40%
 - For the same 13 patients, there would be 80% power to detect a treatment effect of .85 SD, still a fairly large effect
 - http://hedwig.mgh.harvard.edu/sample_size/size.html is the source of this power calculation for a crossover study, using the SD of the difference between two values for the same patient as the basis of the calculation
- Because mild TBI is the most common type in the workers' compensation population, more information is needed about modafinil in this group before a statement about evidence of its effectiveness

Assessment: high quality methodologically, but inadequate for evidence concerning therapeutic value of modafinil (underpowered for the population of interest)