

Modafinil (Provigil®) Use in Fatigue: 2015 Update

Criteria for Use

VHA Pharmacy Benefits Management Services, Advisory Panel and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient. Individual cases that are outside the recommendations should be adjudicated at the local facility according to the policy and procedures of its P&T Committee and Pharmacy Services.

EXCLUSION CRITERIA (If selected, patient is NOT eligible)

- Hypersensitivity to modafinil, armodafinil, or any component of the product

INCLUSION CRITERIA (all bold criteria must be met)

- Other causes of fatigue or excessive daytime sleepiness have been ruled out and appropriately treated (including anemia, hypothyroidism, and depression)**
- AND**
- Patients have received counseling on proper sleep hygiene measures and have implemented such measures prior to consideration of pharmacologic treatment**
https://vaww.portal.va.gov/sites/OMHS/cbt_insomnia/patienthandouts/GuidetoOvercomingYourInsomnia.docx

INDICATIONS (all criteria must be met for each indication):

- Excessive daytime sleepiness associated with **narcolepsy**
 - Clinical diagnosis of narcolepsy
 - Patient must have documented excessive daytime sleepiness (Epworth score > 10) during waking hours⁶
- Excessive sleepiness associated with **shift- work sleep disorder (SWD)**
 - Requirements above for narcolepsy and
 - Patient must have worked more than 5 night shifts per month for at least 3 consecutive months
 - Night shift is defined as ≥ 6 hours between the times of 2200 and 0800
- Excessive daytime sleepiness associated with **obstructive sleep apnea (OSA)** despite optimal treatment by a sleep specialist/pulmonologist or neurologist
 - Clinical diagnosis of obstructive sleep apnea
 - Patient must have documented excessive daytime sleepiness (Epworth score > 10) during waking hours⁶
 - Documented compliance (CPAP use >4hours/ night) and maximized treatment with CPAP for an adequate period of time
- Treatment of fatigue in patients with **multiple sclerosis (MS)**
 - Clinical diagnosis of multiple sclerosis
 - Contraindication or lack of therapeutic response/intolerance to amantadine therapy
 - Based on results from the use of modafinil in treatment of MS related fatigue, the maximum dose is 200 mg daily
- Treatment of fatigue and excessive daytime sleepiness in patients with **active cancer**
 - Clinical diagnosis of cancer and undergoing chemotherapy
 - Patient must have documented excessive daytime sleepiness (Epworth score > 10) during waking hours⁶ and severe fatigue (Brief Fatigue Inventory, question #3 score ≥ 7)
 - Patient has been counseled on the risk of nausea and vomiting associated with modafinil use with concurrent chemotherapy
 - Based on trial results from the use of modafinil in treatment of cancer related excessive daytime sleepiness, the maximum dose is 200 mg daily
- Treatment of excessive daytime sleepiness in patients with **traumatic brain injury (TBI)**
 - Clinical diagnosis of traumatic brain injury
 - Patient must have documented excessive daytime sleepiness (Epworth score > 10) during waking hours⁶

PRESCRIPTION LIMITS AND MONITORING

- All indications will be limited to an initial 30 day supply
- After the 30 day trial, documentation of tolerability and efficacy needs to be noted in the patient's chart in order to continue modafinil. The same clinical measure used to diagnose the fatigue must be repeated to demonstrate efficacy. The testing results must be documented in the patient chart
- The effectiveness of modafinil in long-term use (greater than 4 weeks in cancer clinical trials, 9 weeks in narcolepsy clinical

trials, 10 weeks in TBI trials and 12 weeks in OSA and SWD clinical trials) has not been systematically evaluated. Long-term usefulness should be reevaluated every 6 months using the same clinical measure used to diagnose the fatigue.

ISSUE FOR CONSIDERATION

Abuse Potential- modafinil, produces psychoactive and euphoric effects, alterations in mood, perception, thinking and feelings typical of other CNS stimulants. Modafinil demonstrates an increase in dopamine levels which influences the brain's reward system in a manner similar to other addictive agents

Twice Daily Dosing When modafinil is given twice daily the following schedule is commonly used, morning and noon or early afternoon. The schedule is not the every 12 hr schedule associated with BID dosing.

Combination therapy with other psychostimulants- there is no evidence to support the use of combination therapy with modafinil. Requests should be adjudicated locally

Geriatric use- elimination of modafinil and its metabolites may be reduced in patients >65 years of age; therefore, consideration should be given to using lower doses in the elderly population

Dosage above 200 mg daily-Dosages of up to 400 mg/day given as a single dose have been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond that of the 200 mg dose

Use for Parkinson's disease related fatigue - results from controlled and noncontrolled trials are conflicting, with inconsistent or no benefit observed in objective sleep and fatigue parameters

Brief Fatigue Inventory⁷

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes No										
1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.										
0 No fatigue	1	2	3	4	5	6	7	8	9	10 As bad as you can imagine
2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during the past 24 hours.										
0 No fatigue	1	2	3	4	5	6	7	8	9	10 As bad as you can imagine
3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during the past 24 hours.										
0 No fatigue	1	2	3	4	5	6	7	8	9	10 As bad as you can imagine
4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with you:										
A. General activity										
0 Does not interfere	1	2	3	4	5	6	7	8	9	10 Completely interferes
B. Mood										
0 Does not interfere	1	2	3	4	5	6	7	8	9	10 Completely interferes
C. Walking ability										
0 Does not interfere	1	2	3	4	5	6	7	8	9	10 Completely interferes
D. Normal work (includes both work outside the home and daily chores)										
0 Does not interfere	1	2	3	4	5	6	7	8	9	10 Completely interferes
E. Relations with other people										
0 Does not interfere	1	2	3	4	5	6	7	8	9	10 Completely interferes

**Modafinil (Provigil®) Criteria for Use in TBI and Cancer Related Fatigue:
Evidence Summary**

February 2015

VHA Pharmacy Benefits Management Services, Advisory Panel and VISN Pharmacist Executives

Issues for Consideration

Modafinil for treatment of excessive daytime sleepiness (EDS) and fatigue in Parkinson's disease (PD) patients

Use of modafinil for treatment of fatigue and EDS in PD patients has been evaluated in small controlled and non-controlled studies. Results from these studies report conflicting data regarding the efficacy of modafinil for treatment of fatigue and EDS in this patient population. The largest clinical trial in this patient population evaluated the efficacy of modafinil (200mg-400mg/day) vs placebo over 4 weeks in 40 PD patients with EDS and fatigue.¹ Baseline Epworth Sleepiness Scale (ESS) scores and Fatigue Severity Scale (FSS) scores were similar between the modafinil vs placebo treatment groups (ESS: 15.8± 3.0 vs 15.9± 3.5; FSS: 4.2±1.6 vs 4.1±1.4). Of a total of 40 subjects (29 men, mean (SD) age 64.8 (11.3) years), randomised to modafinil or placebo, 37 completed the study. Modafinil failed to significantly improve ESS scores compared to placebo (13.5± 4.8 vs 14.5± 4.8, respectively, $p>0.05$). FSS were also unchanged between the modafinil and placebo groups (FSS: 4.1± 1.4 vs 4.1. ± 1.2, respectively, $p>0.05$). There was no statistically significant improvement between the two treatment arms in any outcome measurements.

However, results from a smaller double-blind, placebo-controlled trial of 19 PD patients suggest that modafinil may improve physical fatigability.² In this study fatigue was measured by finger tapping frequency. A significant difference in finger tapping frequency in treatment group (197 vs 185 strikes per minute; $P < 0.05$) was detected. The data showed that there was no improvement in EDS as there was no significant reduction in mean ESS score (6 vs 8.3 at baseline; $P < 0.12$). Data from this trial suggests that while physical fatigue may be improved, treatment with modafinil may not improve objective measurements of symptoms associated with fatigue and daytime sleepiness.

Modafinil for treatment of cancer-related fatigue

Results from 2 pilot studies in which 47 patients with cancer and cancer-related fatigue underwent treatment with modafinil (initial dose 100mg/day, then increased to 200mg/day) suggested a beneficial effect of modafinil on fatigue and EDS. The changes noted in fatigue scale scores and ESS were found to be statistically significant.^{3,4}

However, there have been conflicting results from randomized trials of patients reporting fatigue while undergoing chemotherapy. In a randomized clinical trial of 867 patients reporting fatigue while undergoing cancer treatment, patients were randomly assigned to either receive modafinil 100 mg daily during study cycle 2 (later increased to 200 mg daily after 3 days and continued until day 7 of cycle 4) or matching placebo.⁵ Data was analyzed from 631 participants (315 on treatment with modafinil and 316 on placebo). Modafinil was found to significantly reduce fatigue in patients reporting a high baseline fatigue score (BFI-3 > 7). This subgroup of patients was found to have significant improvements in fatigue scores with modafinil treatment. The modafinil treated group also showed significant improvement in ESS scores ($P=0.002$).

The efficacy of modafinil for use in cancer-related fatigue was also evaluated in 83 patients with metastatic prostate or breast cancer undergoing docetaxel chemotherapy (every 21 days; minimum dose 50 mg/m²).⁶ In this trial, fatigue was evaluated with the fatigue component of the MD Anderson

Symptom Inventory (MDASI). The primary endpoint was cumulative MDASI area under the curve (AUC) during the first 7 days of study medication during treatment period 1 (TP1) and treatment period 2 (TP2). There was no statistically significant difference between the two treatment arms for the primary endpoint (MSADI AUC₃₋₁₀ 35.9 vs 39.6; 95 % confidence interval -8.9, 1.4, p=0.15). Although there was a significant difference was found in TP2 (MDASI AUC₃₋₁₀ 33.8 vs 42.2, p=0.03), potentially indicating a delay in the therapeutic effect of modafinil in cancer-related fatigue. This study also reported that the incidence of grade ≤2 nausea and vomiting was higher in the modafinil arm vs the placebo arm (45.4 vs 25 %).

These same results were not seen in a 2014 RCT of 208 patients reporting fatigue while being treated for advanced NSCLC. In this 4 week study participants were randomly assigned to either receive modafinil 100mg/day or matching placebo x 14days, then modafinil 200 mg or placebo for 14 more days. No statistically significant differences in FACIT-fatigue and ESS scores were found between the two treatment groups. In fact, significant improvements in fatigue scores were reported with both modafinil and placebo treatment groups.⁷

Modafinil for the treatment of TBI related fatigue and EDS

Use of modafinil for the management of fatigue and EDS in patients with TBI has been evaluated in a few small studies.

One randomized, placebo-controlled, 6 week pilot study enrolled 20 patients to evaluate the effectiveness of 100-200 mg modafinil every morning vs placebo.⁸ EDS was measured by ESS scores and fatigue was measured using FSS scores. At the end of the treatment period, the reduction in FSS scores from baseline was higher in the modafinil group compared with placebo. However, this difference was not found to be statistically significant (-0.8 vs no change; P = 0.07). Reduction in ESS scores from baseline was significantly higher in the modafinil group (-2.3 vs 0.7; P = 0.005). Patients who were treated with modafinil stayed awake 1.9 hours longer per day, whereas placebo-treated patients did not reveal an increase of their time awake.

A larger study of 53 patients 1 year post-TBI did not report the same improvement with modafinil treatment. Fatigue and EDS were evaluated in this study using FSS and ESS scores, respectively.⁹ In this double-blind, placebo-controlled cross-over trial, participants were randomly assigned to receive up to 400 mg of modafinil, or equal number of inactive placebo tablets x 10 weeks. A 4-week washout period in which the patients received neither modafinil nor placebo occurred in between cross-over. A total of 46 patients completed the crossover study. There were no statistically significant differences between the treatment arms in the FSS scores at week 4 (-0.5 ± 1.88; P = .80) or week 10 (-1.4 ± 2.75; P = .61). For ESS, average changes were significantly greater with modafinil than placebo at week 4 (-1.2 ± 0.49; P = .02) but not at week 10 (-0.5 ± 0.87; P = .56). Although, it was noted that individual responses to modafinil varied among patients suggesting that modafinil treatment may be of benefit to certain patients.

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