modafinil (Provigil)

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Modafinil (Provigil) was FDA approved in 2007 and is a wakefulness-promoting agent used in narcolepsy, obstructive sleep apnea, and shift work sleep disorder. It is also used off-label for fatigue related to multiple sclerosis and cancer.

Narcolepsy is a sleep disorder characterized by excessive sleepiness, daytime sleepiness, and, in some cases, cataplexy. Treatment of narcolepsy can involve both non-pharmacologic therapy (such as practicing good sleep hygiene or psychosocial support) and medications.

Obstructive sleep apnea (OSA) is a condition in which breathing repeatedly starts and stops during sleep due to an obstruction in the upper airway. There are many risk factors for OSA including age, male gender, and obesity. Treatment of OSA can be treated with non-pharmacologic therapy such as weight loss, continuous positive airway pressure (CPAP), oral appliances (such as mandibular advancement devices), and surgery. Drug therapy is also an option for treating OSA. Pharmacologic strategies

include increasing respiratory drive and reducing airway collapsibility. Patients who have OSA may experience interrupted sleep during the night and, therefore, may experience excessive sleepiness during the day. Treatment for residual excessive sleepiness caused from OSA includes wakefulness-promoting agents such as modafinil and armodafinil.

Shift Work Sleep disorder develops in people who work during the hours typically used for sleep (such as the night shift). A night shift worker, for example, usually works during the night and has to sleep during the day but will often try to stay awake during daylight on their days off. Also, working at night and sleeping during the day disrupts one's circadian rhythm which is an internal, biological process that responds to environmental factors. For example, the body will naturally be awake and alert during daylight and want to sleep when it's dark. Therapy for Shift Work Sleep disorder includes practicing good sleep hygiene (i.e., having a sleep schedule, blocking out light), improving daytime sleep with the use of melatonin or sleep agents, and improving wakefulness when awake (with a medication such as modafinil).

Fatigue is a common characteristic of multiple sclerosis and cancer. Non-pharmacologic therapy includes proper sleep hygiene and exercise. However, patients can oftentimes benefit from drug therapy. There are a handful of agents used for fatigue (such as amantadine, stimulants such as methylphenidate, and wakefulness-promoting agents such as modafinil).

Definitions

"Actigraphy" is a device worn on the wrist (like a watch) that measures activity and rest levels to assess sleep patterns and circadian rhythms.

"Cancer-related fatigue (CRF)" is defined as a "distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning."

"Continuous positive airway pressure (CPAP)" is a device that supplies a constant and steady flow of air pressure into the airways to maintain their openness during sleep, commonly used for the treatment of obstructive sleep apnea.

"Hypocretin-1" is a naturally occurring chemical in the brain that plays a crucial role in regulating wakefulness and sleep.

"Mandibular advancement device" is a medical device that is placed in the mouth during sleep to reposition the lower jaw and tongue, helping to keep the airways open and reducing symptoms of obstructive sleep apnea.

"Multiple sleep latency test (MSLT)" is a diagnostic sleep study used to measure the time it takes an individual to fall asleep during the daytime. It assesses daytime sleepiness and can aid in the diagnosis of conditions such as narcolepsy. This is performed following a polysomnography (PSG) performed the night before.

"Polysomnography (PSG)" is a comprehensive sleep study that monitors various physiological parameters during sleep, including brain activity, eye movements, heart rate, oxygen levels, and respiratory patterns. It is used to diagnose and evaluate several sleep disorders. It is usually performed at an attended Sleep Lab facility.

"Sleep latency" refers to the amount of time it takes an individual to fall asleep after lying down and attempting to sleep. It is commonly assessed during sleep studies and can be used as an indicator of sleep quality and sleep disorders.

Medical Necessity Criteria for Initial Authorization

The Plan considers **modafinil** medically necessary when **ALL** the following criteria are met for the applicable indication listed below:

Cancer-related fatigue

1. The member is 18 years of age or older; ***AND***
2. The member has cancer-related fatigue; ***AND***
3. The member has advanced disease or is currently receiving active treatment; ***AND***
4. The member is unable to use, or has tried and failed non-pharmacological strategies (such as physical activity, psychosocial interventions, mind-body interventions).

Fatigue related to Multiple Sclerosis

1. The member is 18 years of age or older; ***AND***
2. The member has a confirmed diagnosis of fatigue due to multiple sclerosis; ***AND***
3. The member has demonstrated excessive daytime sleepiness associated with their MS-related fatigue***; AND***

4. The member has tried and failed non-pharmacological strategies (such as exercise, cooling methods, and cognitive behavioral therapy); ***AND***
5. The member is unable to use, or has adequately tried and failed at least **TWO** (2) of the following medications at their maximum tolerated doses, each for a minimum duration of 30 days:
    a. Amantadine; ***and/or***
    b. Stimulants (such as dextroamphetamine-amphetamine, methylphenidate).

<u>Idiopathic Hypersomnia:</u>

1. The member is 17 years of age or older; ***AND***
2. The member has a confirmed diagnosis of idiopathic hypersomnia; ***AND***
3. Other potential causes of hypersomnia have been ruled out through comprehensive neurological, psychiatric, and other investigations; ***AND***
4. Non-pharmacological approaches, including behavioral strategies and sleep hygiene improvements, have been attempted but have not provided significant improvement in daytime function; ***AND***
5. The member requires treatment to improve excessive daytime sleepiness and functional impairment.

<u>Major Depressive Disorder (MDD)</u>

1. The member is 18 years of age or older; ***AND***
2. The member has a diagnosis of Major Depressive Disorder (MDD) confirmed by a psychiatric evaluation based on DSM-5 criteria; ***AND***
3. The member has been experiencing persistent symptoms of fatigue and sleepiness despite being on a standard antidepressant therapy for at least 8 weeks; ***AND***
4. The member is currently on an antidepressant regimen and has shown partial or no response to standard treatment, or has intolerable side effects; ***AND***
5. The member has tried and failed, or is unable to use at least **TWO** (2) of the following augmentation therapies, each for a minimum duration of 6 weeks:
    a. Atypical antipsychotics (such as aripiprazole, quetiapine, or risperidone)***; and/or***
    b. Antidepressants from a different class than the primary therapy (such as bupropion or mirtazapine); ***AND***
6. A trial of cognitive behavioral therapy or another form of psychotherapy has been attempted and has been insufficient or inappropriate.

Narcolepsy

1. The member is 17 years of age or older; ***AND***
2. The member has a diagnosis of narcolepsy confirmed by Multiple Sleep Latency Test (MSLT) or Cerebrospinal fluid (CSF) hypocretin-1 laboratory test; ***AND***
3. The member has daily periods of excessive daytime sleepiness occurring for at least three months.

Obstructive Sleep Apnea (OSA)

1. The member is 17 years of age or older; ***AND***
2. The member has a diagnosis of obstructive sleep apnea, confirmed by polysomnography or a home sleep apnea test; ***AND***
3. The member is currently using conventional therapy and has been adherent to such therapy, including **ONE** of the following:
    a. Positive Airway Pressure Therapy (such as CPAP)***; or***
    b. Oral Appliances (such as mandibular advancement devices).

Parkinson's Disease–Related Excessive Daytime Sleepiness

1. The medication is prescribed by or in consultation with a neurologist or sleep specialist***; AND***
2. The member is 18 years of age or older***; AND***
3. The member has a confirmed diagnosis of Parkinson's disease***; AND***
4. The member suffers from excessive daytime sleepiness as determined by an Epworth Sleepiness Scale (ESS) score of 10 or higher***; AND***
5. The member's excessive daytime sleepiness is not adequately controlled by other Parkinson's disease treatments or non-pharmacological interventions (such as structured sleep hygiene and regular physical activity)***.***

Shift Work Sleep Disorder (SWSD)

1. The member is 18 years of age or older; ***AND***
2. The member has a diagnosis of Shift Work Sleep Disorder***; AND***
3. Non-pharmacological therapies have been tried and failed, such as setting a sleep schedule and improving sleep hygiene.

If the above prior authorization criteria are met, modafinil will be approved for 12 months.

Medical Necessity Criteria for Reauthorization:

Reauthorization for 12 months will be granted if **ALL** of the following are met:

1. The member still meets the applicable initial criteria***; AND***
2. Chart documentation shows that the member has continued to experience a clinical improvement in symptoms since starting modafinil. For each specific condition, the following criteria apply:
    a. For narcolepsy, obstructive sleep apnea, shift work sleep disorder, Parkinson's disease-related excessive daytime sleepiness, or idiopathic hypersomnia, the member demonstrates ongoing reduction in symptoms of excessive daytime sleepiness.
    b. For fatigue related to multiple sclerosis or cancer-related fatigue, the member shows sustained improvement in excessive daytime sleepiness associated with fatigue.
    c. For major depressive disorder, the member demonstrates sustained improvement in symptoms of fatigue and sleepiness despite being on a standard antidepressant therapy**,**

Experimental or Investigational / Not Medically Necessary

Modafinil for any other indication is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven.

Appendix

Cancer-Related Fatigue, Severe (in Patients Receiving Active Treatment)

There is some evidence supporting the use of modafinil for severe CRF in patients receiving active cancer treatment, particularly in those with severe baseline fatigue. However, more extensive research is needed to confirm these findings, and its use should be considered in conjunction with other non-pharmacologic and pharmacologic interventions for managing CRF. Patient-specific factors including co-existing medical conditions, concomitant medications, and the patient's overall clinical situation should be taken into account when considering modafinil for this indication.

1. The American Society of Clinical Oncology (ASCO) guidelines recommend a multimodal approach to the treatment of CRF, which can include the use of pharmacologic interventions such as psychostimulants (e.g., methylphenidate) and wakefulness agents like modafinil. However, these guidelines also note that there is limited evidence regarding the effectiveness of these agents in reducing fatigue in patients who are disease-free following active treatment.
2. A randomized, double-blind, placebo-controlled phase 3 trial showed a statistically significant benefit of modafinil in patients with severe baseline fatigue receiving active cancer treatment.

Modafinil 200 mg daily was administered to patients starting from day 5 of cycle 2 to day 7 of cycle 4 of their treatment, and the drug was found to improve fatigue scores more than placebo in this patient group. Notably, this effect was not seen in patients with mild or moderate baseline fatigue, indicating that the benefits of modafinil might be specific to those with severe CRF. There was no statistically significant effect of modafinil on depression.

3. While these results are promising, it should be noted that the study was specific to a population of patients undergoing chemotherapy, and its findings might not be generalizable to all cancer patients or to patients who are disease-free post-treatment.

Idiopathic Hypersomnia

1. Evidence from small, randomized, double-blind, placebo-controlled trials of limited duration has demonstrated the efficacy of modafinil for treating idiopathic hypersomnia.
2. The American Academy of Sleep Medicine's (AASM) guideline titled "Treatment of Central Disorders of Hypersomnolence" strongly recommended modafinil for the treatment of idiopathic hypersomnia in adults.
3. In addition to idiopathic hypersomnia, the AASM guideline conditionally suggests the use of modafinil for managing hypersomnia secondary to Parkinson's disease, traumatic brain injury, myotonic dystrophy, multiple sclerosis in adults, and narcolepsy in pediatric patients.

Major Depressive Disorder (Antidepressant Augmentation)

Major depressive disorder, characterized by symptoms such as fatigue, sleepiness, and concentration difficulties, is often inadequately managed by antidepressants alone. This has led to the exploration of augmentation therapies like modafinil, which exhibits stimulant-like properties. While modafinil is not a first-line adjunctive treatment for major depressive disorder, current evidence supports its beneficial effects, especially for managing excessive fatigue and sleepiness. However, additional large-scale, high-quality randomized trials are needed to solidify its role in this context.

1. Several independent double-blind, randomized, placebo-controlled trials have shown beneficial effects of modafinil when added to standard antidepressant therapy in the context of major depressive disorder characterized by excessive fatigue and sleepiness.
2. The Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines classify modafinil as a second-line adjunctive agent. These guidelines recommend its use as an alternative option for patients not fully responding to standard antidepressant treatment.
3. A meta-analysis of six randomized, placebo-controlled trials investigated the efficacy of modafinil or its R-enantiomer, armodafinil, in managing depressive episodes in adult patients. This included patients with unipolar major depressive disorder and bipolar depression.

a. Results indicated a significant improvement in overall depression scores and remission rates when modafinil was added to standard therapy, compared to placebo alone.
b. There was considerable heterogeneity among the studies, suggesting variations in study design, patient populations, or both could have influenced outcomes.
c. Analysis of the four trials focused on unipolar major depressive disorder showed a positive, though not quite statistically significant, effect with modafinil augmentation (p=0.056). When an outlier study was excluded, the remaining evidence demonstrated significant improvements with modafinil (p=0.04).

Multiple Sclerosis–Related Fatigue

The current literature on modafinil for off-label use in MS-related fatigue offers mixed results. A number of studies show beneficial effects, while others suggest there's no significant difference compared to placebo. More high-quality, randomized controlled trials are needed to provide clearer guidance on this issue. Considering the current evidence, modafinil should only be used when other treatments are ineffective, and with careful monitoring for potential side effects.

1. The American Academy of Sleep Medicine (AASM) endorses the use of modafinil for the treatment of hypersomnia secondary to MS. This endorsement is based on a study showing improvement in daytime sleepiness, though the data quality was considered very low.
2. A meta-analysis of five randomized, double-blind trials with 303 participants reported that modafinil was superior to placebo on the Modified Fatigue Impact Scale (MFIS) but showed no significant difference on the Fatigue Severity Scale (FSS) or Symbol Digit Modalities Test (SDMT).
3. Another systematic review and meta-analysis evaluating modafinil's efficacy in treating fatigue associated with neurological disorders failed to find any distinguishable benefit of modafinil over placebo.
4. There have been several controlled trials examining modafinil's efficacy and safety for treating MS-related fatigue. The results have been inconsistent, with some trials finding modest improvements with modafinil while others found no significant difference between modafinil and placebo. There were concerns about adverse events with modafinil in these studies.
5. One single-blind, placebo-controlled, crossover study did find that modafinil at 200 mg/day significantly improved MS-related fatigue and was well-tolerated.

Parkinson Disease–Related Excessive Daytime Sleepiness

The efficacy of modafinil for off-label use in Parkinson's disease-related excessive daytime sleepiness is currently inconclusive, with data from different randomized, double-blind, placebo-controlled trials presenting conflicting results.

1. The American Academy of Sleep Medicine (AASM) suggests the use of modafinil for the treatment of excessive daytime sleepiness secondary to Parkinson's disease based on moderate-quality data from 4 randomized controlled trials and 1 observational study demonstrating significant improvement in excessive daytime sleepiness. However, the AASM's recommendation is a conditional strength recommendation, indicating that different choices may be appropriate for different patients.
2. Two crossover studies suggest that modafinil may be beneficial for improving subjective feelings of excessive daytime sleepiness in patients with Parkinson's disease. In these studies, modafinil modestly improved excessive daytime sleepiness as evaluated by the Epworth Sleepiness Scale (ESS) compared to placebo. In one study, ESS scores increased with placebo but decreased with modafinil. Similarly, in another study, ESS score was significantly improved with modafinil compared to placebo. These studies, however, observed no significant effect of modafinil on other outcome measures, including motor symptoms of Parkinson's disease, fatigue, depression, and capacity to remain awake.
3. A third parallel-design study demonstrated no significant benefit with modafinil compared to placebo. In this trial, the change in ESS score was not significantly different between modafinil and placebo. Similarly, no significant differences were observed between modafinil and placebo for secondary endpoints.

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