Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

OHSU Drug Effectiveness Review Project Summary Report – Off-label Use of Modafinil (Provigil™) and Armodafinil (Nuvigil™)

Date of Review: July 2019

Date of Last Review: September 2015
End Date of Literature Search: 2/8/2019

Current Status of PDL Class:
See **Appendix 1**.

Research Questions:
1. What is the effectiveness of modafinil or armodafinil when prescribed above FDA-approved dosages for approved and off-label indications (e.g., narcolepsy, obstructive sleep apnea [OSA], cancer- or multiple sclerosis [MS]-related fatigue, or major depressive disorder [MDD]?
2. What are the harms of modafinil or armodafinil when prescribed above FDA-approved dosages?

Conclusions:
- There is insufficient comparative evidence for efficacy or harms for either modafinil and/or armodafinil in doses exceeding current FDA labeling for OSA, cancer- or MS-related fatigue and MDD (**Table 1**).[1]

Modafinil
- Two trials of fair methodologic quality with modafinil dosing beyond current FDA labeling (200 to 400mg) for narcolepsy demonstrated improvement in morning and midday sleep latency with statistical and clinical significance as compared to placebo (**Table 1**). However, caution is warranted in interpreting these findings given their low grade of evidence (**Table 1**).[1]
- There was no difference between the two modafinil doses at any time point or for any outcome within either investigation aforementioned (**Table 1**).[1]
- As with other stimulants, discontinuation of modafinil resulted in a return of both objective and subjective sleepiness. However, there was not a pattern of amphetamine-like withdrawal symptoms. During the discontinuation phase of this study, no patients reported withdrawal emergent adverse experiences.[1]

Armodafinil
- One trial with poor methodologic quality compared armodafinil 150 and 250 mg/day to placebo in individuals with narcolepsy; however, evidence was insufficient to draw conclusions (**Table 1**).[1]
- Armodafinil has not been studied in children for any medical indication, and use is not recommended in children.[2-5]

Author: Kara Shirley, PharmD, BCPS, BCPP, BCACP and Sarah Servid, PharmD.

Safety

- DRESS (drug reaction with eosinophilia and systemic symptoms), also known as multi-organ hypersensitivity, has been reported with modafinil and armodafinil. Post-marketing reports have included 2 fatalities associated with DRESS and hypersensitivity following recent initiation of armodafinil. Armodafinil should be discontinued at the first sign of rash, skin or mouth sores, blistering or ulceration.[2-5]
- FDA labeling was revised to emphasize the risk of psychiatric symptoms, including suicidal ideation, with use of armodafinil. Symptoms may result in hospitalization and have occurred with any dose (50 to 450 mg daily).[2-5]

Recommendations:

- No changes to the preferred drug list (PDL) are recommended for modafinil or armodafinil based on the current review of efficacy and safety data.
- Update safety edits to include assessment of first-line therapy in patients with OSA and alternative options for treatment in children.

Summary of Prior Reviews and Current Policy

- Previous reviews have not identified clinically significant comparative differences in efficacy or harms between modafinil and/or armodafinil. There is insufficient evidence on health outcomes (i.e., wakefulness, executive functioning, adverse reactions) as well as off-label dosage consideration to delineate any changes to preferred or non-preferred status. Currently both medications are designated as voluntary non-preferred on the Oregon Health Plan (OHA) preferred drug list (PDL) (**Appendix 1**).
- In an analysis of Oregon Medicaid claims data in 2015, funded off-label diagnoses were associated with 26.5% of patients prescribed armodafinil or modafinil. This data prompted implementation of the current policy that limits modafinil and armodafinil use to FDA approved or evidence-based dosages and indications.
- Current safety edits for modafinil and armodafinil require a 90-day trial with evidence of efficacy for continued use (**Appendix 4**) and 74% of utilization is for modafinil with 26% utilization for armodafinil within the FFS population.

Methods:

The March 2019 drug class report on the Off-label Use of Modafinil (Provigil™) and Armodafinil (Nuvigil™) by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at Oregon Health & Science University (OHSU) was synthesized to inform recommendations for this drug class and written summary. The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

Summary Findings:

Both armodafinil and modafinil are often prescribed above FDA maximum dose and for off-label conditions including fatigue associated with cancer, MS and other neurological conditions, depression, and other mood disorders. An evaluation of modafinil prescriptions in the U.S. (between 2002 and 2009) found that 89% of prescriptions were for off-label conditions.[1] In Oregon Medicaid, prior authorization (PA) requests for modafinil and armodafinil currently account for approximately 5% of all PAs evaluated, and a significant proportion of providers request therapy above the FDA-recommended maximum dose. An analysis of efficacy and/or harms related to modafinil and armodafinil therapy with high, off-label dosage regimens was completed by DERP in March of 2019 to evaluate appropriateness of current dosage limits.[1] A search ending in February 2019 identified 13 studies which compared on-label and off-label dosages (5 RCTs and 8

uncontrolled interventional trials): 7 in individuals with narcolepsy, 1 in individuals with obstructive sleep apnea (OSA), 2 in individuals with multiple sclerosis (MS), and 3 in individuals with depression (MDD partial responders).[1]

For inclusion within the DERP report, trials were required to compare at least 2 different dosages of modafinil or armodafinil. If medication was compared solely to a placebo or the comparative dosages did not exceed the current FDA maximum, the investigation was subsequently excluded from the DERP summary.[1] Two RCTs were graded as having fair methodological quality and the remaining 11 studies graded are of poor methodological quality.[1] Quality grades are reflective of industry involvement in all of the studies included (e.g., funding, study conduct).[1] Additionally, studies were further downgraded because of poor or unclear reporting of methods, no control group, small numbers of participants, brevity of study duration and follow-up, lack of intention-to-treat analysis, and lack of statistical adjustment for differences in baseline characteristics.[1] Few published studies followed up beyond a short treatment period (e.g., 2 to 3 weeks); therefore, it is challenging to conclude whether adverse events were acute or chronic or whether efficacy is sustained over long-term treatment.[1] Studies with results comparing efficacy of different dosages are detailed in **Table 1**.

Studies included within the DERP report evaluated excessive daytime sleepiness as a primary treatment outcome measure.[1] Common tests used to evaluate excessive daytime sleepiness included the clinician-rated multiple sleep latency test (MSLT), the maintenance of wakefulness test (MWT), and the patient-rated Epworth Sleepiness Score (ESS).[1] Additional clinical outcomes evaluation scales are detailed in **Table 1** and **Appendix 3 Table 2**.[1]

Table 1. Modafinil & Armodafinil: Studies with results reported by dose[1]

Comparison	Study Design & Population	Outcome	Clinical Findings	Evidence Strength
Narcolepsy				
U.S. Modafinil in Narcolepsy Multicenter Study Group (1998) Modafinil: 200 mg Modafinil: 400 mg Placebo	RCT; 9 weeks + up 40 weeks of open-label extension N = 283 • Adults 18–68 years • MSLT score < 8 minutes • Age (mean years): 42 • Gender (female): 54.4%	• Wakefulness (ESS, MSLT, MWT) • Clinical condition (CGI-C) • Adverse events	Outcomes evaluated at 9 weeks; mean ± SD **MWT** • 200 mg: 8.1 ± 6.1 minutes (compared to placebo p < 0.001) • 400 mg: 8.9 ± 6.2 minutes (compared to placebo p < 0.001) • Placebo: 5.1 ± 4 7 minutes (results only reported in figure; NS from baseline) **ESS** • 200 mg: 14.4 ± 5.7 minutes (compared to placebo p < 0.001) • 400 mg: 13.0 ± 5.7 minutes (compared to placebo p < 0.001) • Placebo: 17.0 ± 5.0 minutes (compared to baseline p <0.001) **MSLT** • 200 mg: 4.7 ± 4.4 minutes (compared to placebo p < 0.001) • 400 mg: 5.2 ± 4.5 minutes (compared to placebo p < 0.001) • Placebo: 3.3 + 3.2 minutes (results only reported in figure; NS from baseline) **CGI-C (percentages only available in publication figure)** • 200mg: weeks 3,6,9 and endpoint p < 0.005 • 400mg: weeks 3,6,9 and endpoint p < 0.005	**Fair**

<table>
<tr><td></td><td></td><td></td><td>• Placebo: NS (clinical or statistical) in any group at any time; weeks 3,6,9 and endpoint</td><td></td></tr>
<tr><td>U.S. Modafinil in Narcolepsy Multicenter Study Group (2000)
Modafinil: 200 mg
Modafinil: 400 mg
Placebo</td><td>RCT; 9 weeks + up 40 weeks of open-label extension
N = 271
• Adults 17–67 years
• MSLT score ≤ 8 minutes
• ≥ 2 sleep onset REM periods
• No prior modafinil use
• Age (mean years): 42
• Gender (female): 54.4%</td><td>• Wakefulness (ESS, MSLT, MWT)
• Clinical condition (CGI-C)</td><td>Outcomes evaluated at 9 weeks; mean ± SD
MWT
• 200 mg: 8.2 ± 5.9 minutes (placebo and baseline p <0.001)
• 400 mg: 7.8 ± 5.3 minutes (placebo and baseline p <0.001)
• Placebo: 5.5 ± 4.5 minutes (results only reported in figure; NS from baseline)

ESS
• 200 mg: 13.0 ± 5.1 minutes (placebo and baseline p < 0.001)
• 400 mg: 12.3 ± 5.1 minutes (placebo and baseline p < 0.001)
• Placebo: 15.8 ± 4.8 minutes (change from baseline p < 0.001)

MSLT
• 200 mg: 4.9 ± 4.3 minutes (placebo p < 0.001; change form baseline p < 0.03)
• 400 mg: 5.1 ± 4.0 minutes (placebo and baseline p < 0.001)
• Placebo: 3.5 ± 3.4 minutes (change from baseline p < 0.001)

Patients with CGI-C improvement from baseline:
<table><tr><td></td><td>No change</td><td>Minimal</td><td>Much</td><td>Very Much</td></tr><tr><td>400 mg</td><td>29%</td><td>27%</td><td>27%</td><td>9%</td></tr><tr><td>200 mg</td><td>33%</td><td>23%</td><td>26%</td><td>6%</td></tr><tr><td>Placebo</td><td>47%</td><td>24%</td><td>14%</td><td>0%</td></tr></table></td><td>Fair</td></tr>
<tr><td colspan="5">Obstructive Sleep Apnea</td></tr>
<tr><td>Modafinil for Obstructive Sleep Apnea (OSA)
Black et al. (2005)
Modafinil: 200 mg
Modafinil: 400 mg
Placebo</td><td>RCT
12 weeks + 12-month open-label extension
N = 309

• Aged 18–70 years,
• ESS score ≥ 10,
• using nCPAP therapy
• Age (mean years):48.4
• Gender (female):22.4%</td><td>• Wakefulness (MWT, ESS)
• Clinical condition (CGI-S, CGI-C)
• Sleep-related functional status (FOSQ)
• Nighttime sleep and nCPAP use (PSG)
• Adverse events</td><td>MWT
• 1.6 minutes and 1.5 minutes (P > 0.15) between dosages
ESS
• both dosages had a drop of 4.5 points compared to placebo (p-value NS)
CGI-C
• 200mg: 61%
• 400mg: 68%
• Placebo 37%
• 200mg vs. 400 mg: 7% (p-value not reported)
• 200 mg vs. placebo: 24% (P<0.001).
FOSQ (change from baseline for patients given modafinil)
• 6 months SD ± 2.43 ± 2.67 (p < 0.0001)
• 12 months SD ± 2.08 ± 2.71 (p < 0.0001)
Adverse Events (Top 3 for each dosage regimen & placebo)
• Headache 13 to 26% (p=0.02 combined modafinil vs placebo respectively)
• Nausea 2% to 10% (p=0.01 for combined modafinil vs placebo respectively)
• Infection 22% to 10% (p=0.1 combined modafinil vs placebo respectively)</td><td>Poor</td></tr>
</table>

Abbreviations: CGI-C: Clinical Global Impression of Change scale; CGI-S: Clinical Global Impression of Severity scale; ESS: Epstein Sleepiness Scale; FOSQ: Functional Outcomes of Sleep Questionnaire; MSLT: Multiple Sleep Latency Test; MWT: Maintenance of Wakefulness Test; nCPAP = nasal continuous positive airway pressure; NS = nonsignificant; RCT: randomized controlled trial; SD: standard deviation; PSG: polysomnography;

Armodafinil

Narcolepsy

One double-blind RCT of poor quality evaluated armodafinil 150 and 250 mg/day compared to a placebo in individuals with narcolepsy for 12 weeks.[1] Individuals diagnosed with narcolepsy were required to have a rating of "moderately ill" (i.e., ≥4 on the Clinical Global Impression of Severity scale [CGI-S]) and a mean sleep latency of less than or equal to 6 minutes on the MSLT.[1] Due to inadequate statistical power, statistical differences for alleviation of excessive daytime sleepiness, fatigue, or overall clinical condition could not be evaluated between active dosage regimens. Upon comparison of 150mg and 250mg, there was no difference in the proportion of patients who had minimally, much, and very much improvement on the Clinical Global Impression of Change (CGI-C) scale from baseline to 12 weeks (21% vs. 20% for minimal, 33% vs. 35% for much, and 16% vs. 18% for very much improvement for 150 mg and 250 mg, respectively).[1] Comparatively, in patients randomized to placebo, 17% had minimal improvement, 12% were much improved, and 3% were very much improved. Both armodafinil doses were associated with statistically significant improvements in memory, attention, and fatigue as measured by the MWT.[1] The mean change in Maintenance of Wakefulness (MWT) from baseline at final visit for armodafinil was an increase of 1.3, 2.6, and 1.9 minutes from baseline in the 150 mg, 250 mg, and combined groups, respectively, compared with a decrease of 1.9 minutes for placebo ($p < 0.01$ for all three active treatments vs. placebo). Adverse reactions reported more commonly with armodafinil compared to placebo were headache, nausea, and dizziness.[1] Dose-dependent differences in cardiovascular function (e.g., blood pressure) were observed, but differences were small and the clinical significance of these small mean changes is unclear.[1]

Other Indications

At the time of this DERP Summary Report is no published evidence for armodafinil doses greater than or equal to 250 mg/day for OSA, MS-related fatigue, cancer-related fatigue, or depression.[1]

Modafinil

Narcolepsy

Five RCTs (4 parallel group trials and one crossover trial) and one uncontrolled interventional study in narcoleptic individuals evaluated modafinil dosages ranging from 200 to 600 mg/day.[1] Of the 5 RCTs, 3 had poor and 2 had fair methodological quality, and only 2 parallel group RCTs directly compared dose effects.[1] While most studies included in the DERP report were of poor quality, this summary focuses primarily on the fair quality trials. Further detail regarding modafinil narcolepsy studies of poor methodologic quality may be found within the full DERP report.[1]

The U.S. Modafinil in Narcolepsy Multicenter Study Group (1998) was a double-blind, parallel-group, placebo-controlled RCT of modafinil in narcolepsy patients (n=283). Patients were 18 to 68 years of age with a current diagnosis of narcolepsy based on the International Classification of Sleep Disorders.[1] Patients were included if they met the following criteria: 1) recurrent daytime naps or lapses into sleep occurring almost daily for at least 3 months, 2) sudden bilateral loss of postural muscle tone in association with intense emotion (cataplexy), and 3) less than 8 minutes of sleep latency on the MSLT. All participants had 2 or more sleep onset rapid eye movement periods and were free of medical or behavioral health conditions that could account for narcolepsy symptoms. The primary study endpoints were MWT and CGI-C compared to placebo, and secondary outcomes included CGI-S, ESS, and MSLT. Outcomes were measured at 3, 6, and 9 weeks. The percentage of subjects with improved independent clinician assessment of illness on the CGI-C was statistically and clinically significant for the

modafinil 200-mg and 400-mg treatment groups compared with placebo at weeks 3, 6, and 9 and at endpoint (all $p < 0.005$).[1] The percentage of subjects improving on the CGI-C at any timepoint did not differ between the two modafinil groups.[1] The percentage of placebo subjects who improved was also not significant at any assessment at weeks 3, 6 and 9 as compared to baseline.

Modafinil consistently reduced daytime sleepiness on all sleep measures (MWT, MSLT and ESS) and clinician assessment of improvement (CGI-C) compared to placebo, but there was no difference between 200 mg and 400 mg groups (**Table 1**).[1] The MSLT results indicated a magnitude, representativeness, and stability of effect similar to the ESS findings for all treatment groups.[1] Compared to placebo, more subjects in both the modafinil 200 mg and 400 mg treatment groups succeeded in remaining awake for an entire 20-minute MWT test both ($p=0.002$).[1] At baseline, only 3% of those receiving 400 mg modafinil, 4% of those receiving 200 mg modafinil, and 3% of those receiving placebo were able to remain awake for at least three tests. At week 9, the percentage of subjects able to stay awake for at least three MWT tests significantly increased to 20% for the 400 mg modafinil group and 14% for the 200 mg modafinil group in contrast to the placebo group which did not change.[1] Only headache was clinically although not considered statistically significant in a comparison of modafinil to placebo.[1]

A second randomized, placebo-controlled, double-blind, parallel-group trial evaluated two fixed doses of modafinil (200mg and 400mg) compared to placebo.[1] Study assessments were conducted at baseline, at weeks 1, 3, 6, and 9 of the double-blind treatment phase, and at week 2 of the discontinuation phase (week 11 of the study). The primary study endpoints of excessive daytime sleepiness and over clinical condition were assessed using the MWT and CGI-C at baseline and week 9.[1] At baseline, the median time to sleep onset at baseline was approximately 5 minutes. The percent of patients with improved clinician assessment of illness on the CGI-C was greater for modafinil 200 mg (46/80 patients, 58%) and 400 mg treatment groups (51/83 patients, 61%) compared with placebo (32/84 patients, 38%) at week 9 ($p=0.03$ for comparisons to placebo; **Table 1**).[1] The percentage of patients who improved was also greater in both modafinil groups at weeks 3 and 6 as compared to baseline ($p>0.05$). The percent of patients who improved in the modafinil 400 mg treatment group was not significantly greater than the percent of patients who improved in the 200 mg treatment group (**Table 1**).[1] The percent of patients who improved in the placebo treatment group was not statistically or clinically significant at any post baseline CGI-C assessment.[1]

During the 9-week treatment phase, patients in the modafinil 200 mg and 400 mg groups demonstrated a statistically and clinically significant increase in wakefulness as measured by the MWT, ESS, and MSLT compared to placebo but no clinical difference between 200 mg and 400 mg doses (**Table 1**).[1] Although modafinil was an effective therapeutic agent and improved alertness in a profoundly sleepy population, it did not completely resolve the symptoms of EDS **(Table 1)**, and treatment was associated with a significant placebo response (all groups improved in subjective sleepiness [ESS] from baseline; **Table 1**).[1] As with other stimulants, discontinuation of modafinil resulted in a return of both objective and subjective sleepiness. In some cases, rebound symptoms after treatment discontinuation were more severe than symptoms reported at baseline. During the discontinuation phase, there was no observed pattern of amphetamine-like withdrawal symptoms or withdrawal emergent adverse experiences.[1]

Obstructive Sleep Apnea

One open-label extension study of poor methodologic quality compared modafinil at 200 and 400 mg/day for 12 months in 266 participants with OSA (104 additional participants received a placebo).[1] Those who met study inclusion criteria had diagnosed OSA using nasal continuous positive airway pressure (CPAP) and had completed at least 8 weeks of a 12-week double blind treatment period where ESS baseline screening was greater than or equal to 10.[1] Treatment with modafinil at 200 or 400 mg/day increased sleep latency and reduced subjective excessive daytime sleepiness as compared to placebo ($P < 0.0001$) with clinical and statistical significance (CGI-C and FOSQ; **Table 1**).[1] The Functional Outcomes Sleep Questionnaire (FOSQ) assessed the impact of excessive daytime sleepiness (EDS) on functional outcomes relevant to daily activities and quality of life, whereby lower scores indicate greater dysfunction.[1] Modafinil maintained the patients' functional status, as shown by a significant improvement compared with baseline in the mean FOSQ total score (change from baseline ± SD at 6

months was 2.43 ± 2.67 and at 12 months was 2.08 ± 2.71; both $p < 0.0001$), as well as individual domains of activity level, vigilance, intimacy/sexual relationship, general productivity and social outcome (all $p < 0.0001$).[1] However, there were no clinically or statistically significant differences in measurements of EDS including mean MWT (1.6 vs. 1.5 minutes; $P > 0.15$) or ESS ($P > 0.15$; data not reported) between the two modafinil dosages (**Table 1**).[1] Similarly, there was no difference in overall clinical condition, as measured by the CGI-C, between the 2 modafinil dosages (61% for 200mg and 68% for400mg; **Table 1**).[1] The majority of adverse events were assessed as mild or moderate in severity.[1] Anxiety, nervousness and insomnia occurred in 14 patients and serious adverse events were reported in 13 patients, one of which experienced bradycardia and syncope (**Table 1**).[1]

Fatigue secondary to Multiple Sclerosis (MS)

Two uncontrolled interventional studies of poor methodological quality compared modafinil 200 and 400 mg/day in individuals with MS (n=122; 50 open-label trial and 72 crossover investigation).[1] Many findings from these investigations were published in figure form only and should also be interpreted with caution given their poor methodological quality.[1] Overall, reductions in MS associated sleepiness (ESS) and fatigue (FSS, BFI and VAS-F) were not observed at high doses of 400mg/day compared to baseline. However, in patients prescribed modafinil doses of less than 200mg improvement in sleepiness from baseline was documented.[1] Common adverse events associated with modafinil for MS associated fatigue were headache, anxiety and vertigo. A total of 9 participants discontinued treatment due to adverse events.[1]

Augmentation of Depression "Partial-Responders"

Three studies (one RCT and 2 uncontrolled trials) of poor methodologic quality examined modafinil 50 to 400 mg/day for augmentation of major depression in patients prescribed at least one antidepressant.[1] The majority of participants in these studies received 300 mg/day.[1] Trials did not report results by dosing regimen making valid statistical and/or clinical comparison difficult.[1] In the RCT, there was no statistically significant difference between modafinil and placebo for wakefulness (ESS), fatigue (ESS), overall clinical condition (CGI-C), and depression (HAM-D and MADRS) after 6 weeks of adjunctive modafinil therapy.[1] In a 12-week, uncontrolled open-label extension study evaluating benefit of dose increases in patients on 200 mg modafinil, 69 patients (28%) previously nonresponsive to modafinil at dosages of 200 mg/day found that they had clinically significant therapeutic response in fatigue symptom scores (FSS) and wakefulness (ESS) at dosages of 300 to 400 mg/day. These results were not statistically significant.[1] Common adverse events of modafinil in all depression augmentation studies included headache, anxiety, insomnia, nausea and dizziness (**Table 1**).[1]

Cancer-related Fatigue

No trials were identified for modafinil in dosages greater than or equal to 200 mg/day for cancer-related fatigue.[1]

New FDA Safety Alerts:

Table 2. Description of new FDA Safety Alerts[12]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Armodafinil	Nuvigil®	February 2017	Warnings/Precautions	Serious dermatologic reactions, Drug Reaction with Eosinophilia and System Symptoms (DRESS) and multiorgan hypersensitivity were added to labeling based on postmarketing reports. Post-marketing reports have included 2 fatalities associated with DRESS and hypersensitivity following recent initiation of armodafinil. Armodafinil should be discontinued at the first sign of rash, skin or mouth sores, blistering or ulceration.

				Labeling was also revised to emphasize the risk of psychiatric symptoms, including suicidal ideation, with use of armodafinil. Symptoms may result in hospitalization and have occurred with any dose (50 to 450 mg daily).

References

1. Robalino S, Anderson R, Harrod C. Off-label use of modafinil (Provigil™) and armodafinil (Nuvigil™). Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2019.
2. Sateia M. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014 Nov;146(5):1387-1394. doi: 10.1378/chest.14-0970.
3. Epstein LJ, Kristo D, et al. American Academy of Sleep Medicine—Clinical Guideline for the Evaluation, Management, and Long-term Care of Obstructive Sleep Apnea in Adults (2009). Clin Sleep Med. 2009 Jun 15;5(3):263-76. https://aasm.org/resources/clinicalguidelines/osa_adults.pdf
4. Ruoff C, Rye D. The ICSD-3 and DSM-5 guidelines for diagnosing narcolepsy: clinical relevance and practicality, Current Medical Research and Opinion (2016), 32:10, 1611-1622, https://doi.org/10.1080/03007995.2016.1208643
5. Raggi A, Plazzi G, et al. Health-Related Quality of Life in Patients With Narcolepsy: A Review of the Literature. The Journal of Nervous and Mental Disease. 2019 Feb;207(2):84–99. doi: 10.1097/NMD.0000000000000918. PMID: 30672873
6. Morgenthaler TI, Kapur VK, et al. American Academy of Sleep Medicine—Practice Parameters for the Treatment of Narcolepsy and other Hypersomnias of Central Origin (2007) Sleep. 2007 Dec;30(12):1705-11. http://aasm.org/resources/practiceparameters/pp_narcolepsy.pdf
7. Sullivan SS, Kushida CA. Multiple sleep latency test and maintenance of wakefulness test. Chest. 2008 Oct;134(4):854-61. doi: 10.1378/chest.08-0822.
8. Goldbart A, Peppard P, et al.. Narcolepsy and predictors of positive MSLTs in the Wisconsin Sleep Cohort. SLEEP 2014;37(6):1043-1051.
9. Pizza F, Jaussent I et al. Car Crashes and Central Disorders of Hypersomnolence: A French Study. PLoS One. 2015 Jun 8;10(6):e0129386. doi: 10.1371/journal.pone.0129386. eCollection 2015.
10. Popp RF, Fierlbeck AK, et al. Daytime sleepiness versus fatigue in patients with multiple sclerosis: A systematic review on the Epworth sleepiness scale as an assessment tool. Sleep Med Rev. 2017 Apr;32:95-108. doi: 10.1016/j.smrv.2016.03.004. Epub 2016 Mar 18.
11. Scrima L, Emsellem HA, et al. Identifying clinically important difference on the Epworth Sleepiness Scale: results from a narcolepsy clinical trial of JZP-110. Sleep Med. 2017 Oct;38:108-112. doi: 10.1016/j.sleep.2017.07.006. Epub 2017 Jul 22. DOI: 10.1016/j.sleep.2017.07.006
12. Nuvigil (Armodafinil) FDA Safety-related labeling changes Approved by FDA Center for Drug Evaluation and Research (CDER) 02/07/2017 (SUPPL-23) https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=828
13. Nuvigil (Armodafinil) FDA Supplemental Approval Letter to Cephalon, Inc. FDA Center for Drug Evaluation and Research (CDER) 02/07/2017 (SUPPL-23) https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/021875Orig1s023ltr.pdf
14. Provigil prescribing information. Cephalon Inc., Frazier, PA. January 2015. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020717s037s038lbl.pdf. Accessed April 4, 2019
15. Nuvigil prescribing information. Cephalon Inc., Frazier, PA. April 2015. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021875s021lbledt.pdf. Accessed April 4, 2019

Appendix 1: Current Preferred Drug List

V	armodafinil	TABLET
V	armodafinil (NUVIGIL)	TABLET
V	modafinil	TABLET
V	modafinil (PROVIGIL)	TABLET

Appendix 2: PICOS

Population	Individuals with narcolepsy, obstructive sleep apnea, cancer-related fatigue, multiple sclerosis-related fatigue, or depression
Intervention	Modafinil prescribed above 200 mg/day or armodafinil prescribed above 250 mg/day
Comparator	Any dosage of modafinil or armodafinil or placebo
Outcomes	**Symptom Improvement** Reduction in excessive daytime sleepiness and/or fatigue, psychiatric symptoms **Safety** Misuse and dependence potential Serious Adverse Events Discontinuation from Serious Adverse Events
Timing	Any study duration; literature search through February 8, 2019
Setting	Outpatient

Appendix 3: Summary of Outcomes Rating Scales of Clinical Significance in DERP Report

Questionnaire/Test	*Rater*	*Scale*	*Clinical Significance*
Narcolepsy & OSA			
Maintenance of Wakefulness Test (MWT)[1,6-8]	Clinician	Mean sleep latency on the 40 minutes MWT of < 8 minutes = abnormal and 8 to 40 minutes are of uncertain significance. Direction of change may also serve as a clinical guide in Narcolepsy as well as OSA.	Objectively assesses the ability to remain awake for a defined period of time in a laboratory setting (quiet non-stimulating situation for a given period of time). Concurrent driving simulation testing adds real-world predictive value in occupational assessment. Also used to evaluate individuals who must stay awake for job safety reasons however may not accurately predict performance in real-life circumstances.
Multiple Sleep Latency Test (MSLT)[1, 6-8]	Clinician	Measures an individual's ability to fall asleep in the laboratory setting. The Multiple Sleep Latency Test (MSLT) is a sleep disorder diagnostic tool. It is used to measure the time elapsed from the start of a daytime nap period to the first signs of sleep, called sleep latency. The test is based on the idea that the sleepier people are, the faster they will fall asleep. The test consists of four or five 20-minute nap opportunities set two hours apart, often following an overnight sleep study. During the test, data such as the patient's brain waves, EEG, muscle activity, and eye movements are monitored and recorded. The entire test normally takes about 7 hours during the course of a day.	Mean sleep latency of less than 5 minutes indicates a pathologic level of daytime sleepiness. Normal adults have a mean sleep latency of 10 to 20 minutes. Sleep latency on the screening MSLT < 3min usually indicates marked or severe EDS although distinct sleep latency cutoffs have not been statistically validated due population differences. Can be influenced by sleep up to 7 days before the test the preceding sleep-wake cycle. Interpretation relies on AASM established scoring criteria (last in 2007) inclusive of mean sleep latency of all naps as well as onset to REM sleep.
Epworth Sleepiness Scale (ESS)[11]	Patient	Total scores range from 0 to 24, with higher scores indicating greater sleepiness. Eight scenarios rated from 0 to 3 in terms of how likely the patient feels they would be to fall asleep.	Score is the sum of questions from 8 proposed situations. Higher score indicates increased daytime sleepiness; An ESS score ≥ 10 indicates ES and requires further assessment. An improvement in wakefulness is indicated by a decrease in score.
Clinical Global Impression of Change Scale (CGI-C)[1]	Clinician	CGI-C scores range from 1 (very much improved) through to 7 (very much worse). "Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment."	Each component of the CGI is rated separately; the instrument does not yield a global score.
Functional Outcomes of Sleep Questionnaire (FOSQ)[1]	Patient	Thirty (30) items, 5 factor subscales. Disease specific quality of life questionnaire to determine functional status in adults; measures are designed to assess the impact of disorders of excessive sleepiness on multiple activities of everyday living and the extent to which these abilities are improved by effective treatment.	Activity level, vigilance, intimacy and sexual relationships, general productivity, social outcome, rate the difficulty of performing a given activity on a 4-point scale (no difficulty to extreme difficulty). Lower scores indicate greater dysfunction.
MS-Related Fatigue			
Modified Fatigue Impact Scale (MFIS)[1, 10]	Patient	0 to 84 (lower score indicates less fatigue). The total score for the MFIS is the sum of the scores for the 21 items. Individual subscale scores for physical, cognitive, and psychosocial functioning can also be generated by calculating the sum of specific sets of items.	The MFIS is a modified form of the Fatigue Impact Scale based on items derived from interviews with MS patients concerning how fatigue affects their lives. This instrument provides an assessment of the effects of fatigue in terms of physical, cognitive, and psychosocial functioning.
Visual Analogue Scale for Fatigue (VAS-F)[1, 10]	Patient	0 to 100 (higher score indicates less fatigue) Two subscales: fatigue (items 1–5 and 11–18) and energy (items 6–10). Though individuals do not require training in order to score the scale, developers are quick to point out that high levels of inter-rater reliability are vital if results are to be correctly interpreted.	Consists of 18 items relating to the subjective experience of fatigue. Each item asks respondents to place an "X," representing how they currently feel, along a visual analogue line that extends between two extremes (e.g., from "not at all tired" to "extremely tired"). In contrast to discrete, Likert-type scales, the VAS-F places fewer restrictions on the range of responses available to individuals. However, the benefits of a visual analogue scale may be offset by the frequent reluctance of individuals to use the highest and lowest extremes.

Brief Fatigue Inventory (BFI)[1, 10]	Patient	Patients rated each item using an 11-point scale (0–10), with higher scores indicating greater fatigue severity or impact.	Patient-rated global fatigue (average of all questions) and worst fatigue during the past 24h (Item number 3).
Fatigue Severity Scale of Sleep Disorders (FSS) [1,10]	Patient	Nine (9) statements that rate the severity of fatigue symptoms. Each statement is scored from 1 to 7, based on how accurately it reflects the patient's condition during the past week and the extent to which the patient agrees or disagrees. A low value (e.g., 1) indicates strong disagreement with the statement, whereas a high value (e.g., 7) indicates strong agreement.	Total score of less than 36 suggests that the patient may not be suffering from fatigue. A total score of 36 or more suggests that the patient may need further evaluation.
Clinical Global Impression of Severity Scale (CGI-S)[1]	Clinician	The CGI is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients).	Each component of the CGI is rated separately; the instrument does not yield a global score.
Depression			
Hamilton Depression Rating Scale (HAM-D)[1]	Clinician	Method for scoring varies by version. For the HDRS17, a score of 0–7 is generally accepted to be within the normal range (or in clinical remission), while a score of 20 or higher (indicating at least moderate severity) is usually required for entry into a clinical trial.	The HDRS (also HAM-D) is the most widely used clinician-administered depression assessment scale. Originally developed for hospital inpatients, thus the emphasis on melancholic and physical symptoms of depression. *A later 21-item version (HDRS21) included 4 items intended to subtype the depression, but which are sometimes, incorrectly, used to rate severity. A limitation of the HDRS is that atypical symptoms of depression (e.g., hypersomnia, hyperphagia) are not assessed.*
Montgomery Asberg Depression Rating Scale (MADRS)[1]	Clinician	Used by clinicians to assess the severity of depression among patients with a diagnosis of depression. It is designed to be sensitive to change resulting from antidepressant therapy. Takes 20-60 minutes to be completed by interview. MADRS is typically interview administered, however it can be self-administered. The MADRS should be used with caution in patients with cognitive impairment as results can be skewed towards higher depression scores, however the MADRS can be used with individuals with aphasia.	Each item has a severity scale from 0 to 6, with higher scores reflecting more severe symptoms. Ratings can be added to form an overall score (from 0 to 60). Scores of 0-6 indicate an absence of symptoms; 7-19 represent mild depression; 20-34 moderate; 35-60 indicate severe depression.
Abbreviations: BFI: Brief Fatigue Inventory; CGI-C: Clinical Global Impression of Change scale; CGI-S: Clinical Global Impression of Severity scale; EEG: Electroencephalogram; ESS: Epstein Sleepiness Scale; FSS: Fatigue Severity Scale; FOSQ: Functional Outcomes of Sleep Questionnaire HAM-D: Hamilton Rating Scale for Depression; MADRS: Montgomery-Asberg Depression Rating Scale; MFIS: Modified Fatigue Impact Scale; MSLT: Multiple Sleep Latency Test; MWT: Maintenance of Wakefulness Test; nCPAP: nasal continuous positive airway pressure; QD: single dose; SD: split dose; VAS-F: Visual Analogue Scale for Fatigue			

Modafinil / Armodafinil (Sleep-Wake Medications)

Goal(s):

- Limit use to diagnoses where there is sufficient evidence of benefit and uses that are funded by OHP. Excessive daytime sleepiness related to shift-work is not funded by OHP.
- Limit use to safe doses.

Length of Authorization:

- Initial approval of 90 days if criteria met; approval of up to 12 months with documented benefit OR doses above those in Table 2.

Requires PA:

- Payment for drug claims for modafinil or armodafinil without previous claims evidence of narcolepsy or obstructive sleep apnea

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Funded Indications.

Indication	Modafinil (Provigil™)	Armodafinil (Nuvigil™)
• Excessive daytime sleepiness in narcolepsy • Residual excessive daytime sleepiness in obstructive sleep apnea patients treated with CPAP.	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older
• Depression augmentation (unipolar or bipolar I or II acute or maintenance phase) • Cancer-related fatigue • Multiple sclerosis-related fatigue	Not FDA approved; Low level evidence of inconsistent benefit	Not FDA approved; insufficient evidence
• Drug-related fatigue • Excessive daytime sleepiness or fatigue related to other neurological disorders (e.g. Parkinson's Disease, traumatic brain injury, post-polio syndrome) • ADHD • Cognition enhancement for any condition	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence

Table 2. Maximum Recommended Dose (consistent evidence of benefit with lower doses).

Generic Name	Minimum Age	Maximum FDA-Approved Daily Dose
armodafinil	18 years	250 mg
modafinil	18 years	200 mg

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the patient 18 years of age or older?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness. Providers for patients 7 to 17 years of age may also submit a request for sodium oxybate as it is FDA- approved for narcolepsy in this age group.
3. Is this a funded diagnosis? Non-funded diagnoses: • Shift work disorder (ICD10 G4720-4729; G4750-4769; G478) • Unspecified hypersomnia (ICD10 G4710)	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by OHP
4. Is the drug prescribed by or in consultation with an appropriate specialist for the condition (e.g., sleep specialist, neurologist, or pulmonologist)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Will prescriber consider a preferred alternative?	**Yes:** Inform prescriber of preferred alternatives (e.g., preferred methylphenidate)	**No:** Go to #6

Approval Criteria		
6. Is the request for continuation of therapy at maintenance dosage previously approved by the FFS program?	**Yes:** Go to Renewal Criteria	**No:** Go to #7
7. Is the prescribed daily dose higher than recommended in Table 2?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #8
8. Is the request for treatment of narcolepsy?	**Yes:** Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	**No:** Go to #9
9. Is the request for treatment of obstructive sleep apnea (OSA) (without narcolepsy) and is the patient compliant with recommended first-line treatments (e.g., CPAP)?	**Yes:** Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	**No:** Go to #10
10. Is the request for armodafinil?	**Yes:** Pass to RPh. Deny; medical appropriateness. There is insufficient evidence for off-label use.	**No:** Go to #11
11. Is the primary diagnostic indication for modafinil fatigue secondary to major depression (MDD), MS or cancer-related fatigue? Note: Methylphenidate is recommended first-line for cancer.	**Yes:** Inform prescriber of first-line options available without PA. May approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit and assessment of adverse effects.	**No:** Go to #12

Approval Criteria
12. All other diagnoses must be evaluated as to the OHP-funding level and evidence for clinical benefit. • Evidence supporting treatment for excessive daytime sleepiness (EDS) or fatigue as a result of other conditions is currently insufficient and should be denied for “medical appropriateness”. • Evidence to support cognition enhancement is insufficient and should be denied for “medical appropriateness”. If new evidence is provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.

Renewal Criteria		
1. Is the request for treatment of obstructive sleep apnea?	**Yes:** Go to #2	**No:** Go to #3
2. Is the patient adherent to primary OSA treatment (e.g.,CPAP) based on chart notes?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is there documentation of clinical benefit and tolerability from baseline? The same clinical measure used to diagnose excessive daytime sleepiness (EDS), fatigue secondary to MS and/or cancer, major depressive disorder (MDD) is recommended to document clinical benefit.	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T Review: *7/19; 03/16; 09/15*
Implementation: *8/19/19; 8/16, 1/1/16*