

## Drug Use Evaluation: modafinil and armodafinil

### Research Questions:

- What is the overall Oregon Health Plan (OHP) utilization trend of modafinil and armodafinil from 2014 to present?
- What was the impact on utilization of the dose and age limits implemented in September 2014?
- What diagnoses are most commonly associated with OHP patients with modafinil and armodafinil drug claims?
- What is the evidence for efficacy and safety of modafinil and armodafinil for the most prevalent diagnoses and are they funded by OHP?

### Conclusions:

- The number of OHP patients with claims for either drug has increased 40% over the 15 months from January 2014 to March 2015 and 14% per 1000 members per month. The attention deficit hyperactivity disorder (ADHD) drug class ranked 3rd by net cost in quarter 1 of 2015 and modafinil ranked 26th.<sup>1</sup>
- The absolute number (31 vs. 6) and the rate (23.3% vs 4.4%) of patients newly started on modafinil or armodafinil and that exceeded recommended doses dramatically decreased after the prior authorization policy was implemented. The number of pediatric patients were very low initially (n=2) and increased slightly (n=4) after the age limit was implemented. The net cost of modafinil and armodafinil was \$560,000 in quarter 3 of 2014<sup>2</sup> but dropped to \$300,000 in quarter 1 of 2015.<sup>1</sup>
- The most common diagnoses were organic sleep apnea (35.8%), narcolepsy (19.0%), all depressions combined (19.0%), attention deficit hyperactivity disorder (7.1%) and multiple sclerosis (5.6%). The highest association by diagnostic group was to funded FDA diagnoses (45.9%). Funded off-label diagnoses were associated with 26.5% of patients. Only 4.1% had only a non-funded diagnosis of interest but, there was no diagnosis of interest associated with 23.5% of patients.
- There is moderate level evidence modafinil and armodafinil statistically improves sleep latency in patients with narcolepsy or with continuous positive airway pressure (CPAP) treated obstructive sleep apnea as measured by the Multiple Sleep Latency Test and the Maintenance of Wakefulness Test. The clinical relevance of the seemingly modest mean differences is debatable.<sup>3,4,5</sup> No normal sleep latency has been established, there is a wide range of sleep latency among healthy people and the degree of change that is clinically significant has not been established.<sup>6</sup> Treatment guidelines indicate obstructive sleep apnea be first treated with CPAP or mandibular advancement devices.<sup>5</sup>
- There is insufficient evidence for armodafinil for any off-label use evaluated here.
- There is low level and inconsistent evidence of short-term benefit of modafinil for fatigue associated with multiple sclerosis,<sup>7,8,9</sup> cancer<sup>9,10</sup> and anti-psychotic use.<sup>11</sup> Despite the low level evidence, consensus based guidelines recommend its use for both multiple sclerosis- and cancer-related fatigue.<sup>12</sup> There is insufficient evidence of modafinil efficacy for fatigue associated with other conditions.
- There is low level evidence from small, heterogeneous and poorly controlled trials that modafinil used as augmentation treatment improves short-term depression scores.<sup>13,14,15</sup> There is low evidence of inconsistent benefit for residual fatigue in patients responsive to antidepressants or mood stabilizers.<sup>16</sup>
- There is insufficient and inconsistent evidence of modafinil for adult ADHD.<sup>17,18</sup> The data are more robust, but still low level for pediatrics.
- There are reports of potential use for cognition enhancement with little supporting evidence.<sup>19,20,21</sup>

**Recommendations:**

- Implement a prior authorization for patients initiated on modafinil or armodafinil (no claims evidence within 102 days) and without previous claims evidence of narcolepsy or obstructive sleep apnea (ICD9:347.00-347.01327.20-327.21, 327.23-327.29, 780.51, 780.53, 780.57). See Proposed PA criteria **Appendix 4**. Grandfather current modafinil/armodafinil users for 1 year.

**Background:**

Modafinil<sup>22</sup> and armodafinil<sup>23</sup> are both approved by the United States Food and Drug Administration (FDA) for treatment of excessive somnolence associated with narcolepsy, obstructive sleep apnea and shift work sleep disorder. They are also used extensively off-label with varying levels of evidence (**Appendix 1**). The OHP currently funds treatment of obstructive sleep apnea and narcolepsy but does not fund treatment of shift work disorder.<sup>24</sup> A prior authorization (PA) of excessive doses (>250 mg of armodafinil or > 200mg of modafinil) and use in patients younger than 18 was implemented in September of 2014.<sup>25</sup> The net cost of modafinil and armodafinil was \$560,000 in quarter 3 of 2014<sup>2</sup> but dropped to \$300,000 in quarter 1 of 2015.<sup>1</sup> The ADHD class ranked 3<sup>rd</sup> by net cost in quarter 1 of 2015 and modafinil ranked 26th.<sup>1</sup>

Modafinil and armodafinil (the R enantiomer of modafinil) produce alterations in mood, perception, thinking and feelings that are typical of central nervous system stimulants but differ from the sympathomimetic amines in pharmacological profile.<sup>26,27</sup> Modafinil and armodafinil stimulate discrete brain regions rather than broad brain activation.<sup>26,27</sup> They also do not bind to norepinephrine, serotonin, dopamine, gamma-aminobutyric acid, adenosine, histamine 3, melatonin, or benzodiazepine receptors, nor do they inhibit monoamine oxidase-B or phosphodiesterases II through V.<sup>26,27</sup> The mechanism of action is still unknown.<sup>26,27</sup> Modafinil and armodafinil appear to be well tolerated, with the main adverse effects being headache and nausea.<sup>26,27</sup>

Narcolepsy is characterized primarily by excessive daytime sleepiness with involuntary episodes of falling asleep and frequently includes episodes of cataplexy.<sup>28</sup> It can also include sleep paralysis, hallucinations at sleep initiation or awakening or disturbed nighttime sleep.<sup>28</sup> The prevalence is estimated to be 25 per 100,000 in white populations.<sup>29</sup> The majority of cases have no discernable secondary cause and are first diagnosed from age 15 to 35 years old.<sup>28</sup> It is a life-long illness that can affect all aspects of life quality.<sup>29</sup> Scheduled sleep periods (daytime napping plus regular bedtime) is recommended and may reduce symptom severity.<sup>28</sup> Modafinil is recommended first-line for daytime sleepiness<sup>29</sup> based upon a 9 week randomized trial (n=271) comparing modafinil 400 mg versus 200 mg versus placebo. Sleep latency was evaluated using the Multiple Sleep Latency Test and the Maintenance of Wakefulness Test.<sup>3</sup> At baseline the mean Multiple Sleep Latency Test score in minutes was 2.7, 3.0 and 2.2 respectively, and at 9 weeks was 5.1 (p < 0.001), 4.9 (p = 0.03) and 3.5.<sup>3</sup> The Maintenance of Wakefulness Test was 5.9, 6.1 and 6 minutes at baseline and increased to 7.8 (p < 0.001), 8.2 (p < 0.001) and 5.5 minutes at 9 weeks.<sup>3</sup> Armodafinil was studied in 196 patients aged 18-65 years who were randomized to armodafinil 150 mg versus armodafinil 250 mg versus placebo once daily for 12 weeks. Change in mean Maintenance of Wakefulness Test at 12 weeks was +1.3 minutes, +2.6 minutes and -1.9 minutes (p < 0.01).<sup>4</sup> The clinical relevance of the statistical, but seemingly modest differences on objective sleep measures by modafinil and armodafinil is debatable. No normal sleep latency has been established, there is a wide range of sleep latency among healthy people and the degree of change that is clinically significant has not been established.<sup>6</sup> Methylphenidate has been recommended second line treatment for excessive daytime sleepiness based upon lower levels of evidence for efficacy.<sup>29</sup>

Obstructive sleep apnea is a sleep disorder where the upper airway is obstructed causing repeated complete or partial apnea and resulting in frequent awakenings and poor sleep.<sup>30</sup> One cohort study of 1149 adults from Cleveland, estimates the 5-year incidence to be 10% - 16%.<sup>5</sup> Risk factors include obesity and older age.<sup>5</sup> Complications of untreated obstructive sleep apnea include cardiovascular disease and increased risk of motor vehicle accidents.<sup>5</sup> The Maintenance of Wakefulness Test does not reliably predict safer drivers.<sup>5</sup> Treatment recommendations include weight reduction for overweight patients, correction of positional apnea issues, CPAP and mandibular advancement devices to reduce the apneic episodes and improve sleep quality.<sup>5</sup> There is moderate level evidence that modafinil and armodafinil may reduce residual daytime sleepiness in CPAP treated patients.<sup>5</sup> The studies are limited by subjective measures and the unknown clinical relevance of statistical difference over placebo.

The goals of this drug use evaluation are to describe overall utilization trends, assess the effectiveness of the age and dose restrictions implemented in September 2014 and document the diagnoses associated with patients who use modafinil and armodafinil to inform drug policy.

### **Methods:**

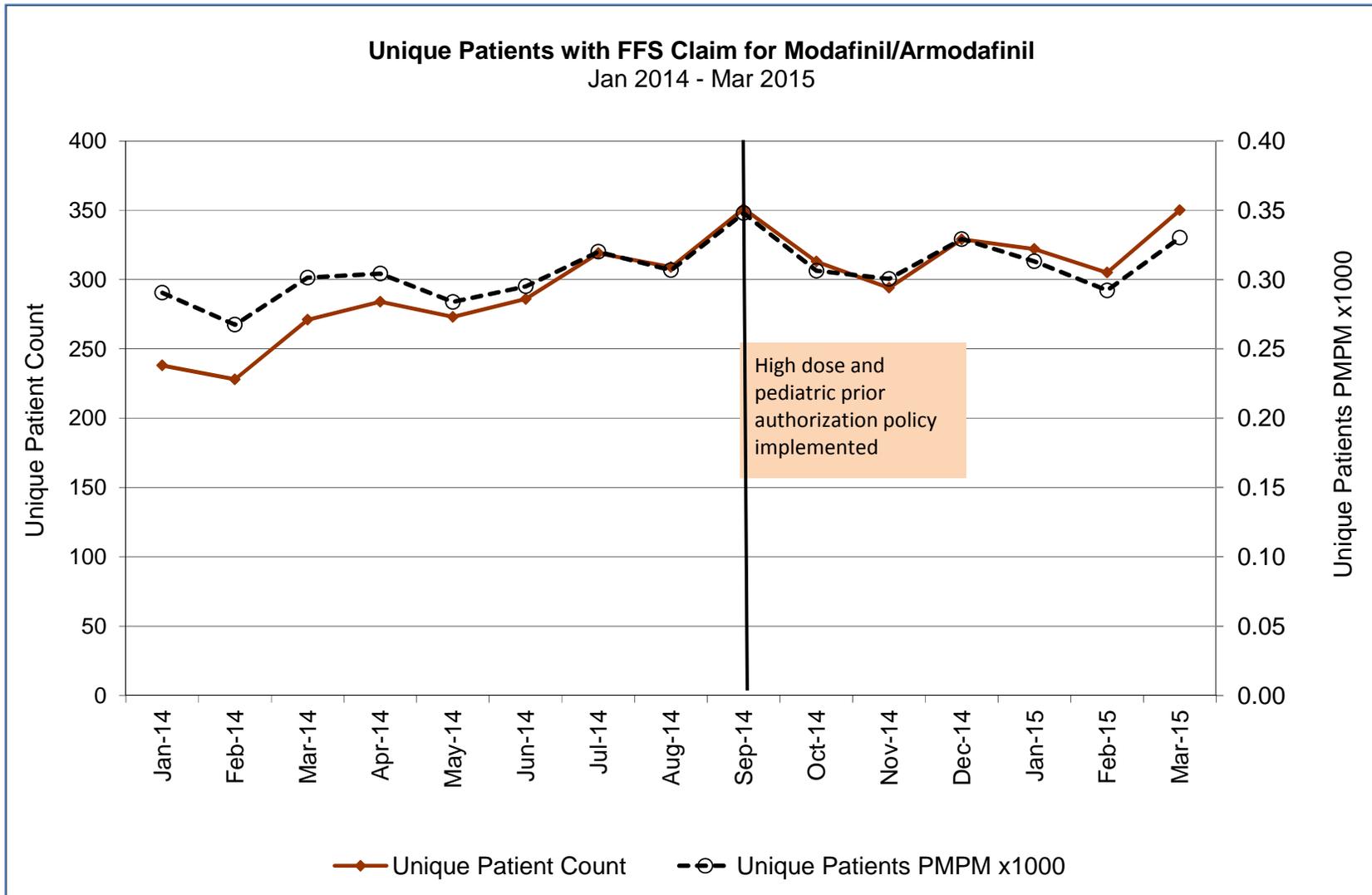
All patients with OHP fee-for-service (FFS) paid drug claims for modafinil (HSN = 010865) or armodafinil (HSN = 034868) from January 1, 2014 through March 30, 2015 were included in the trend analysis. Only patients newly initiated on either drug during quarter 1 of 2014 (Pre-Policy) and quarter 1 of 2015 (Post-Policy) were included in the diagnostic and dose analyses. Newly started patients were identified if they had no prior claim in the 100 days prior to the first drug claim and the first claim was labeled the index event. Patients not initiated during either quarter were excluded. Part D patients identified with drug benefit packages BMM or BMD were excluded. No eligibility length restrictions were applied.

Off-label diagnoses (**Appendix 1**) were identified from Micromedex™ and American Hospital Formulary Service™ and included if there was mid-level evidence of benefit in either reference. Patients were categorized into the diagnostic groups in **Appendix 1** if a diagnosis code occurred on either FFS or encounter medical claim within 5 years prior to and including the date of index event. Patients that exceeded the recommended maximum dose (**Appendix 2**), as calculated using “Dispensed Quantity” divided by “Days Supply”, for any claim during in quarter of 2014 and 2015 were identified.

A Medline™ literature search for systematic reviews or meta-analyses assessing modafinil or armodafinil efficacy or effectiveness for the most prevalent off-label diagnoses (depression, fatigue associated with multiple sclerosis or cancer and attention deficit hyperactivity disorder) was conducted. The Medline™ search strategies used for this review are available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed™, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool.

**Results:**  
 Figure 1 indicates the number of unique patients with claims for either drug has increased 40% over the 15 months from January 2014 to March 2015. When controlled for enrollment, the increase rate drops to 14% per 1000 members per month.

**Figure 1 - Unique Patient Count with Drug Claim for Modafinil or Armodafinil**



After exclusion of Medicare patients, a total of 811 unique patients were identified (348 in the Pre-PA Group and 463 in the Post-PA Group). After limiting to patients newly initiated, the Pre-PA group was 133 and the Post-PA Group was 135. There were 7 patients that met the criteria for both groups. Table 1 displays the demographics of patients initiated on either modafinil or armodafinil before and after the dose and pediatric limit policy was implemented September 2014. The absolute number and rate of pediatric patients actually increased slightly from 2 (1.5%) prior to the PA to 4 (3.0%) after the PA. However, the lowest age increased from 14 to 15 years. In general, the Post-PA group is somewhat younger and more patients are enrolled in coordinating care organizations.

**Table 1: New Modafinil and Armodafinil Patient Demographics**

	Pre-PA		Post-PA	
	133	%	135	%
Mean age (range)	43.3	(14-63)	41.4	(15-65)
<19	2	1.5%	4	3.0%
19-30	16	12.0%	28	20.7%
>30	115	86.5%	103	76.3%
Female	87	65.4%	88	65.2%
White	105	78.9%	113	83.7%
FFS (at index claim)	25	18.8%	12	8.9%

Table 2 displays the number of patients initiated on modafinil or armodafinil who exceeded the maximum recommended dose per day. The absolute number (31 vs. 6) and the rate (23.3% vs 4.4%) dramatically decreased after the prior authorization policy was implemented.

**Table 2: Patients Exceeding Maximum Dose Per Day**

	Pre-Policy		Post-Policy	
	133	%	135	%
Modafinil 200mg daily	27	20.3%	5	3.7%
Armodafinil 250mg daily	4	3.0%	1	0.7%
Total	31	23.3%	6	4.4%

Table 3 displays the selected diagnoses associated with patients on modafinil and armodafinil and puts them in mutually exclusive groups in priority order. The most common diagnoses were organic sleep apnea (35.8%), narcolepsy (19.0%), all depressions combined (19.0%), attention deficit hyperactivity disorder (7.1%) and multiple sclerosis (5.6%). The highest association by diagnostic group was to funded FDA diagnoses (45.9%). Funded off-label diagnoses were associated with 26.5% of patients. Only 4.1% had a non-funded diagnosis of interest but there was no diagnosis of interest associated with 23.5% of patients.

**Table 3: Associated Diagnoses of All New Patients Combined**

Mutually-exclusive groups in priority of 1, 2, 3, 4

	n=	268
<b>FDA Funded Indications (Group 1)</b>	<b>123</b>	<b>45.9%</b>
Narcolepsy	51	19.0%
Organic sleep apnea (except high altitude)	96	35.8%
<b>Funded Off-Label Indications (Group 2)</b>	<b>71</b>	<b>26.5%</b>
Attention deficit hyperactivity disorder	19	7.1%
Depression (unipolar or bipolar)	51	19.0%
Steinert myotonic dystrophy syndrome	0	0.0%
Cancer	2	0.7%
Multiple sclerosis	15	5.6%
<b>Non-Funded Indications (Group 3)</b>	<b>11</b>	<b>4.1%</b>
Narcolepsy in conditions classified elsewhere	0	0.0%
Organic sleep disorders except organic sleep apneas	1	0.4%
Shift work sleep disorder	6	2.2%
Hypersomnia, unspecified	8	3.0%
<b>No Diagnosis of Interest (Group 4)</b>	<b>63</b>	<b>23.5%</b>

A summary of the Medline literature search results, including abstracts is in **Appendix 3**. There were 10 reviews including modafinil or armodafinil for fatigue (2 excluded as not systematic reviews,<sup>31,32</sup> 2 were unavailable<sup>33,34</sup> 1 excluded for irrelevant intervention<sup>35</sup>), 5 reviews for depression (1 excluded for irrelevant outcomes assessed<sup>36</sup> and 1 excluded for irrelevant intervention<sup>37</sup>), 4 reviews for ADHD (2 excluded for intervention irrelevance<sup>38,39</sup>). There were 4 reviews for cognition enhancement<sup>19,20,21,40</sup> and 2 general reviews documenting off-label uses.<sup>41,42</sup> The remaining reviews and those identified from the gray literature sources are discussed below.

## FATIGUE

Cancer (0.7%) and multiple sclerosis (5.6%) was associated new modafinil and armodafinil users. The evidence of efficacy for fatigue related to these conditions and to drug-related sedation is limited and inconsistent.

### Multiple Sclerosis Fatigue

The most recent systematic review included studies that evaluated modafinil treatment versus placebo for fatigue and excessive daytime sleepiness associated with neurological disorders.<sup>7</sup> Eight randomized controlled trials (RCTs) were included: 3 for multiple sclerosis, 2 for Parkinson's Disease, 2 for traumatic brain injury and 1 for post-polio syndrome.<sup>7</sup> The meta-analyses of the 3 multiple sclerosis studies (n=800, 5-8 weeks duration) used the Fatigue Severity Scale and the Modified Fatigue Impact Scale and failed to prove a beneficial effect.<sup>7</sup> The efficacy of modafinil on excessive daytime sleepiness in patients with multiple sclerosis was investigated in two of the studies (n=600, 5-8 weeks duration) and was not confirmed in the pooled studies.<sup>7</sup> The authors conclude that the majority of studies are small and the evidence is insufficient to recommend modafinil for routine treatment for fatigue or excessive daytime sleepiness associated with multiple sclerosis and the other diagnoses that were reviewed.<sup>7</sup>

Six trials (3 open-label, n= 100; 1 single-blind, n=72; and 2 double-blind RCTs n=136) were included in another systematic review of modafinil for treatment of multiple sclerosis-related fatigue.<sup>8</sup> Six different, self-reported symptom scales were used to measure outcomes.<sup>8</sup> Lower doses had positive results in the open-label trials and higher doses did not.<sup>8</sup> Only one of the RCTs found a reduction on the Fatigue Severity Scale at 8 weeks, the other did not.<sup>8</sup> The evidence was conflicting.

### Cancer Fatigue

The Cochrane Collaborative produced a review of pharmacological treatment for fatigue associated with palliative care.<sup>9</sup> There were 45 studies included (n=4696) involving 18 different drugs.<sup>9</sup> There was a very high degree of statistical and clinical heterogeneity in the trials.<sup>9</sup> Studies of modafinil for multiple sclerosis-related fatigue were also included.<sup>9</sup> There was weak and inconclusive evidence for the efficacy of modafinil in multiple sclerosis.<sup>9</sup> Modafinil was evaluated for cancer-related fatigue in 2 studies (n=704) with mixed results.<sup>9</sup> The first found an interaction with baseline fatigue; those with severe fatigue benefited and those with mild or moderate fatigue did not.<sup>9</sup> The second study found that both modafinil and placebo produced a clinically significant improvement and there was no difference between them.<sup>9</sup> The meta-analysis showed an estimated superior effect for methylphenidate in cancer-related fatigue as measured by the Brief Fatigue Inventory instrument (standardized mean difference 0.49, 95% confidence interval (CI) 0.15 to 0.83).<sup>9</sup>

Four trials (2 open-label, 1 RCT with open-label extension, 1 RCT published in abstract only) were included in another systematic review of modafinil for the treatment of cancer-related fatigue.<sup>10</sup> The open-label trials involved 133 breast cancer patients treated for 1 month.<sup>10</sup> The open-label extension trial was in patients with cerebral tumors and the RCT involved 888 patients with unknown cancers.<sup>10</sup> The studies all used different self-reported scales or lacked detail.<sup>10</sup> Published results were statistically significant but of unknown clinical relevance.<sup>10</sup>

### Drug-related Fatigue

A systematic review of modafinil for adjunctive treatment of antipsychotic-related sedation evaluated the evidence from 6 trials (2 RCTs, 3 randomized cross-over trials and 1 open-label).<sup>11</sup> The results were inconsistent with only 1 study finding a significant beneficial effect of treating antipsychotic-induced fatigue. The authors concluded the available trials were too limited by small samples, contradictory results and differences in cognitive testing to draw conclusions.

### *DEPRESSION*

Depression (either unipolar or bipolar) was associated with 19.0% of new modafinil or armodafinil users. Stimulants are used for adjunctive treatment for patients non-responsive to antidepressants or mood stabilizers and also to treat lingering fatigue symptoms in responsive patients. There is low level evidence of short-term improvement of depression scores when added to antidepressants or mood stabilizers. There is insufficient evidence of benefit for residual fatigue symptoms.

### Acute Bipolar Depression

A recent systematic review of all treatments for acute bipolar depression limited study designs to randomized, double-blind and placebo controlled trials with clearly defined outcomes identified 2 studies; 1 of modafinil (n=87, 6 weeks) and 1 of armodafinil (n=257, 8 weeks).<sup>13</sup> Both studies were reported to significantly reduce the Inventory of Depressive Symptomatology score when added to a mood stabilizer. Over half of the participants were also on an antidepressant. Few study details were presented and no author conclusions were drawn from this information.

### Unipolar or Bipolar Depression Augmentation

Another systematic review,<sup>14</sup> criticized by Database of Abstracts of Reviews of Effects<sup>43</sup> as potentially unreliable due to the small, heterogeneous and unclear quality of the evidence base, identified 6 RCTs (n=910) evaluating modafinil: 4 for major depressive disorder (n=568) and 2 for bipolar depression (n=342).<sup>14</sup> Study durations ranged from 6-8 weeks and outcomes were measured using a variety of depression scales.<sup>14</sup> Selective serotonin reuptake inhibitors were the primary treatment in the major depression studies. Lithium was the primary treatment one bipolar study and mood stabilizer with or without antidepressant was used in the other. The results were pooled using the percentage reduction in the various depression scores. The point estimate for the pooled studies was -0.3543 95% CI -0.6071 to -0.1016 p=0.006, I<sup>2</sup> = 67.39%.<sup>14</sup> The authors concluded modafinil is an effective augmentation strategy for acute depressive episodes.<sup>14</sup>

Cochrane published a review of stimulants for depression that was last updated in 2008.<sup>15</sup> It included 5 drugs (dexamphetamine, methylphenidate, methylamphetamine, pemoline and modafinil). Most trials were short-term, up to 6 weeks. Modafinil was evaluated separately due to its unique pharmacology and 3 trials (n=642) were included. The results obtained using fixed effects models suggest that for people with depression, treatment with oral stimulants in comparison with a placebo in the short term (up to 4 weeks) statistically reduces symptoms. The effect was not replicated in the meta-analysis of trials that used modafinil. The authors could draw few clinically relevant conclusions due to the small sample sizes and heterogeneity.

### Residual fatigue after depression treatment

A systematic review included studies where modafinil was used to treat patients with residual fatigue from depression and the effects were measured with validated fatigue subscales.<sup>16</sup> One retrospective, 5 open-label and 2 RCTs were included. Modafinil improved residual fatigue scores in the open-label trials but the results were not confirmed in the RCTs. The open-label trials were limited by small numbers or lack of control. Outcome measures were also inconsistent.

### *ADHD*

ADHD was associated with 7.1% of new of new modafinil or armodafinil users. There are inconsistent results and little evidence to support this use in adults and low level evidence in children.

### Adult ADHD comorbid with mood disorders

The Canadian Network for Mood and Anxiety Treatments task force published a systematic review<sup>44</sup> and treatment recommendations for adult patients with comorbid mood disorders (depression or bipolar disease) with ADHD. This review is comprehensive in nature and includes epidemiology, clinical presentation, neurobiology, and treatment recommendations. Mean comorbidity rates for ADHD and bipolar disease were reported at 12.8%; for ADHD and major depression was reported as 7.8%. These are 3 and 2 times more prevalent than in the general population for adults (i.e. 3%-4%). Modafinil was not assessed in comorbid individuals but there were 2 placebo-controlled studies conducted in adult ADHD patients that demonstrated short-term efficacy. The 2 studies were not described but, they are the same as described in the following review below. Modafinil is recommended second-line after bupropion for adult ADHD comorbid with bipolar disease. This recommendation is made with the caution that there is a potential to destabilize mood during the long-term as there is no data beyond 6 weeks. Modafinil was not recommended for ADHD comorbid with major depression.

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### Adult ADHD

An earlier systematic review of modafinil for ADHD included 4 RCTs.<sup>17</sup> Two were placebo controlled and conducted in children (n= 272) for 6-9 weeks, 1 was a single dose placebo-controlled crossover trial in 20 adults and the last was a phase 3 crossover trial comparing modafinil to dextro-amphetamine in 22 adults for 6 weeks. All used different outcome scales and all showed significant improvements. The populations met ADHD diagnostic criteria but were not required to fail other therapies. Patients were excluded if they had comorbid developmental or psychiatric diagnoses. The authors conclude that modafinil may be viable for some patients for whom the standard ADHD treatment are ineffective or not tolerated but that additional long-term studies are needed.

The Canadian Agency for Drugs and Technologies in Health reviewed non-stimulant therapies (including modafinil) for treatment of adult ADHD.<sup>18</sup> Two studies were included, one of which is the 6 week placebo crossover trial described above. The other was a 9-week, placebo RCT. The authors conclude that the efficacy of modafinil in reducing ADHD symptoms is not statistically significantly different than dextro-amphetamine and superiority over placebo was not consistent across the trials.

## COGNITION ENHANCEMENT

There were 3 systematic reviews<sup>19,20,21</sup> exploring the evidence of modafinil for enhanced cognition. All focused on healthy adults. Each found the evidence gaps to be large and generally conclude that expectations likely exceed the actual drug effect.

### References:

1. Internal Report. OHP FFS Q1-2015 Market Share Report (no 340b). April 2015.
2. Internal Report. OHP FFS Q3-2014 Market Share Report (no 340b). October 2014.
3. Group UM in NMS. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. *Neurology*. 2000;54(5):1166-1175. doi:10.1212/WNL.54.5.1166.
4. Harsh JR, Hayduk R, Rosenberg R, et al. The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy. *Curr Med Res Opin*. 2006;22(4):761-774. doi:10.1185/030079906X100050.
5. Tishler PV, Larkin EK, Schluchter MD, Redline S. Incidence of sleep-disordered breathing in an urban adult population: the relative importance of risk factors in the development of sleep-disordered breathing. *JAMA*. 2003;289(17):2230-2237. doi:10.1001/jama.289.17.2230.
6. Freedman N. Quantifying sleepiness. In: *UpToDate [database online]*. 2015 ed. United States: Wolters Kluwer Health; 2015. [http://www.uptodate-com.liboff.ohsu.edu/contents/quantifying-sleepiness?source=see\\_link#H10](http://www.uptodate-com.liboff.ohsu.edu/contents/quantifying-sleepiness?source=see_link#H10). Accessed June 22, 2015.
7. Sheng P, Hou L, Wang X, et al. Efficacy of Modafinil on Fatigue and Excessive Daytime Sleepiness Associated with Neurological Disorders: A Systematic Review and Meta-Analysis. Paul F, ed. *PLoS ONE*. 2013;8(12):e81802. doi:10.1371/journal.pone.0081802.
8. Brown JN, Howard CA, Kemp DW. Modafinil for the Treatment of Multiple Sclerosis-Related Fatigue. *Ann Pharmacother*. 2010;44(6):1098-1103. doi:10.1345/aph.1M705.
9. Peuckmann V, Elsner F, Krumm N, Trottenberg P, Radbruch L. Pharmacological treatments for fatigue associated with palliative care. [Review]. *Cochrane Database Syst Rev*. 2010. doi:10.1002/14651858.CD006788.pub2.
10. Cooper MR, Bird HM, Steinberg M. Efficacy and Safety of Modafinil in the Treatment of Cancer-Related Fatigue. *Ann Pharmacother*. 2009;43(4):721-725. doi:10.1345/aph.1L532.
11. Saavedra-Velez C, Yusim A, Anbarasan D, Lindenmayer J-P. Modafinil as an Adjunctive Treatment of Sedation, Negative Symptoms, and Cognition in Schizophrenia: A Critical Review. *J Clin Psychiatry*. 2009;70(1):104-112. doi:10.4088/JCP.07r03982.
12. Modafinil. In: *AHFS DI (Adult and Pediatric) In Lexicomp Online [database online]*. 2015 ed. United States: Wolters Kluwer Health; 2015. [http://online.lexi.com.liboff.ohsu.edu/lco/action/doc/retrieve/docid/essential\\_ashp/410736](http://online.lexi.com.liboff.ohsu.edu/lco/action/doc/retrieve/docid/essential_ashp/410736). Accessed June 5, 2015.
13. Cerullo MA, Strakowski SM. A systematic review of the evidence for the treatment of acute depression in bipolar I disorder. *CNS Spectr*. 2013;18(04):199-208. doi:10.1017/S1092852913000102.
14. Goss AJ, Kaser M, Costafreda SG, Sahakian BJ, Fu CHY. Modafinil augmentation therapy in unipolar and bipolar depression: a systematic review and meta-analysis of randomized controlled trials. *J Clin Psychiatry*. 2013;74(11):1101-1107. doi:10.4088/JCP.13r08560.
15. Candy M, Jones L, Williams R, Tookman A, King M. Psychostimulants for depression. [Review] [126 refs]. *Cochrane Database Syst Rev*. 2008. doi:10.1002/14651858.CD006722.pub2.
16. Lam JY, Freeman MK, Cates ME. Modafinil Augmentation for Residual Symptoms of Fatigue in Patients with a Partial Response to Antidepressants. *Ann Pharmacother*. 2007;41(6):1005-1012. doi:10.1345/aph.1H526.
17. Lindsay SE, Gudelsky GA, Heaton PC. Use of Modafinil for the Treatment of Attention Deficit/Hyperactivity Disorder. *Ann Pharmacother*. 2006;40(10):1829-1833. doi:10.1345/aph.1H024.
18. Tricyclic Antidepressants, Clonidine, Venlafaxine, and Modafinil for the Treatment of Attention-Deficit/Hyperactivity Disorder in Adults: A Review of the Clinical Evidence. *Can Agency Drugs Technol Health*. March 2013. <https://www.cadth.ca/tricyclic-antidepressants-clonidine-venlafaxine-and-modafinil-treatment-attention>. Accessed June 24, 2015.
19. Bagot KS, Kaminer Y. Efficacy of stimulants for cognitive enhancement in non-attention deficit hyperactivity disorder youth: a systematic review. [Review]. *Addiction*. 2014;109(4):547-557.
20. Repantis D, Schlattmann P, Laisney O, Heuser I. Modafinil and methylphenidate for neuroenhancement in healthy individuals: A systematic review. [Review]. *Pharmacol Res*. 2010;62(3):187-206. doi:10.1016/j.phrs.2010.04.002.
21. Kelley AM, Webb CM, Athy JR, Ley S, Gaydos S. Cognition enhancement by modafinil: a meta-analysis. *Aviat Space Environ Med*. 2012;83(7):685-690.
22. PROVIGIL® (modafinil) Label. January 2015. [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/020717s037s0381bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020717s037s0381bl.pdf). Accessed June 5, 2015.
23. NUVIGIL® (armodafinil) Label. April 2015. [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/021875s0211bledt.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021875s0211bledt.pdf). Accessed June 5, 2015.
24. Health Evidence Review Commission Prioritized List of health services. <http://www.oregon.gov/oha/herc/Pages/PrioritizedList.aspx>. Accessed June 5, 2015.
25. Oregon Health Authority. Oregon Medicaid Pharmaceutical Services Program Information - Oregon Medicaid PA Criteria, April 2015. *Or Health Auth Med Assist Program*. April 2015. <http://www.oregon.gov/oha/healthplan/tools/Oregon%20Medicaid%20PA%20Criteria,%20April%202015.pdf>. Accessed June 9, 2015.

26. Modafinil. In: *Micromedex Solutions [database online]*. 2015 ed. United States: Truven Health Analytics Inc.; 2015. [http://www.micromedexsolutions.com.liboff.ohsu.edu/micromedex2/librarian/ND\\_T/evidencexpert/ND\\_PR/evidencexpert/CS/97423E/ND\\_AppProduct/evidencexpert/DUPLICATIONSHIELD SYNC/C193F5/ND\\_PG/evidencexpert/ND\\_B/evidencexpert/ND\\_P/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=Modafinil&UserSearchTerm=Modafinil&SearchFilter=filterNone&navitem=searchGlobal#](http://www.micromedexsolutions.com.liboff.ohsu.edu/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/97423E/ND_AppProduct/evidencexpert/DUPLICATIONSHIELD SYNC/C193F5/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=Modafinil&UserSearchTerm=Modafinil&SearchFilter=filterNone&navitem=searchGlobal#). Accessed June 5, 2015.
27. Armodafinil. In: *Micromedex Solutions [on-Line Database]*. Vol 2015th ed. United States: Truven Health Analytics Inc.; 2015. [http://www.micromedexsolutions.com.liboff.ohsu.edu/micromedex2/librarian/ND\\_T/evidencexpert/ND\\_PR/evidencexpert/CS/26CA27/ND\\_AppProduct/evidencexpert/DUPLICATIONSHIELD SYNC/3510F5/ND\\_PG/evidencexpert/ND\\_B/evidencexpert/ND\\_P/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=armodafinil#](http://www.micromedexsolutions.com.liboff.ohsu.edu/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/26CA27/ND_AppProduct/evidencexpert/DUPLICATIONSHIELD SYNC/3510F5/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=armodafinil#). Accessed June 5, 2015.
28. Narcolepsy. In: *DynaMed [database online]*. 2015 ed. United States: EBSCO Information Services; 2014. <http://web.b.ebscohost.com.liboff.ohsu.edu/dynamed/detail?vid=2&sid=e978e5d9-cacb-48f7-98d0-689ee54715e4%40sessionmgr113&hid=106&bdata=JnNpdGU9ZHluYW1lZC1saXZlJnNjb3BIPXNpdGU%3d#db=dme&AN=116132>. Accessed June 13, 2015.
29. Billiard M, Bassetti C, Dauvilliers Y, et al. EFNS guidelines on management of narcolepsy. *Eur J Neurol*. 2006;13(10):1035-1048. doi:10.1111/j.1468-1331.2006.01473.x.
30. Obstructive sleep apnea (OSA): DynaMed. In: *DynaMed [database online]*. 2015 ed. United States: EBSCO Information Services; 2015. <http://web.b.ebscohost.com.liboff.ohsu.edu/dynamed/detail?vid=4&sid=a9393e86-988b-46d0-8ed3-1c8dd4438436%40sessionmgr115&hid=101&bdata=JnNpdGU9ZHluYW1lZC1saXZlJnNjb3BIPXNpdGU%3d#db=dme&AN=115600>. Accessed June 22, 2015.
31. Barsevick AM, Irwin MR, Hinds P, et al. Recommendations for high-priority research on cancer-related fatigue in children and adults. *J Natl Cancer Inst*. 2013;105(19):1432-1440. doi:10.1093/jnci/djt242.
32. Harris J-D. Fatigue in chronically ill patients. [Review] [63 refs]. *Curr Opin Support Palliat Care*. 2008;2(3):180-186. doi:10.1097/SPC.0b013e32830baed0.
33. Carroll JK, Kohli S, Mustian KM, Roscoe JA, Morrow GR. Pharmacologic treatment of cancer-related fatigue. [Review] [75 refs]. *Oncologist*. 2007;43-51.
34. Kirshbaum M. Pharmacologic treatments for fatigue associated with palliative care. [Review]. *J Oncol Nurs*. 2011;15(4):438-439. doi:10.1188/11.CJON.438-439.
35. Jong E, Oudhoff LA, Epskamp C, et al. Predictors and treatment strategies of HIV-related fatigue in the combined antiretroviral therapy era. [Review]. *AIDS*. 2010;24(10):1387-1405. doi:10.1097/QAD.0b013e328339d004.
36. Scoriels L, Jones PB, Sahakian BJ. Modafinil effects on cognition and emotion in schizophrenia and its neurochemical modulation in the brain. [Review]. *Neuropharmacology*. January 2013;168-184. doi:10.1016/j.neuropharm.2012.07.011.
37. Moulton CD, Hopkins C w. p., Bevan-Jones WR. Systematic review of pharmacological treatments for depressive symptoms in Huntington's disease. *Mov Disord*. 2014;29(12):1556-1561. doi:10.1002/mds.25980.
38. Castells X, Ramos-Quiroga JA, Bosch R, Nogueira M, Casas M. Amphetamines for Attention Deficit Hyperactivity Disorder (ADHD) in adults. [Review]. *Cochrane Database Syst Rev*. 2011. doi:10.1002/14651858.CD007813.pub2.
39. Chamberlain SR, Robbins TW, Winder-Rhodes S, et al. Translational approaches to frontostriatal dysfunction in attention-deficit/hyperactivity disorder using a computerized neuropsychological battery. *Biol Psychiatry*. 2011;69(12):1192-1203. doi:10.1016/j.biopsych.2010.08.019.
40. Wood S, Sage JR, Shuman T, Anagnostaras SG. Psychostimulants and cognition: a continuum of behavioral and cognitive activation. [Review]. *Pharmacol Rev*. 2014;66(1):193-221. doi:10.1124/pr.112.007054.
41. Frost J, Okun S, Vaughan T, Heywood J, Wicks P. Patient-reported outcomes as a source of evidence in off-label prescribing: analysis of data from PatientsLikeMe. *J Med Internet Res*. 2011;13(1). doi:10.2196/jmir.1643.
42. Ballon JS, Feifel D. A systematic review of modafinil: Potential clinical uses and mechanisms of action. [Review] [146 refs]. *J Clin Psychiatry*. 2006;67(4):554-566.
43. Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]: Modafinil augmentation therapy in unipolar and bipolar depression: a systematic review and meta-analysis of randomized controlled trials. <http://www.ncbi.nlm.nih.gov.liboff.ohsu.edu/pubmedhealth/PMH0061792/>. Accessed June 22, 2015.
44. Bond DJ, Hadjipavlou G, Lam RW, et al. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid attention-deficit/hyperactivity disorder. *Ann Clin Psychiatry*. 2012;24(1):23-37.
45. Aromodafinil. In: *AHFS DI (Adult and Pediatric) In Lexicomp Online [database online]*. 2015 ed. United States: Wolters Kluwer Health; 2015. [http://online.lexi.com.liboff.ohsu.edu/lco/action/doc/retrieve/docid/complete\\_ashp/3011443](http://online.lexi.com.liboff.ohsu.edu/lco/action/doc/retrieve/docid/complete_ashp/3011443). Accessed June 5, 2015.

**Appendix 1 – Diagnoses of Interest**<sup>27,26,45,12</sup>

Diagnoses	OHP Funded codes
<b>Funded<sup>24</sup> FDA Indications (Group 1)</b>	
Narcolepsy	347.00-347.01
Organic sleep apnea (except high altitude)	327.20-327.21, 327.23-327.29, 780.51, 780.53, 780.57
<b>Funded<sup>24</sup> Off-Label Indications (Group 2)</b>	
Attention deficit hyperactivity disorder: <i>AHFS Level C</i> <i>MM Level B (Adult), A (Pediatric)</i>	314.00-314.9
Depression, Unipolar or bipolar; Adjunct: <i>MM Level B (Adult)</i>	296.20-296.22, 296.25-296.26, 296.90-296.99, 298.0, 311, 625.4
Steinert myotonic dystrophy syndrome: <i>MM Level B (Adult)</i>	359.21
Fatigue in adult cancer survivors: <i>AHFS Level G</i>	140.xx - 209.xx
Multiple sclerosis-related fatigue: <i>AHFS Levels B &amp; G</i> <i>MM Level B</i>	340.xx
<b>Non-Funded<sup>24</sup> Indications (Group 3)</b>	
Narcolepsy in conditions classified elsewhere	347.10 -347.11
Organic sleep disorders except organic sleep apneas	327.00, 327.01, 327.02, 327.09-327.13, 327.14, 327.15, 327.19, 327.22
Shift work sleep disorder	327.30-327.8
Hypersomnia, unspecified <i>Adverse reaction to drug - Somnolence: MM Level B</i> <i>Sleep deprivation: MM Level B (Adult)</i>	780.54
<b>No Diagnosis of Interest (Group 4)</b>	

Micromedex (MM) Evidence Levels:
Category A evidence is based on data derived from: Meta-analyses of randomized controlled trials with homogeneity with regard to the directions and degrees of results between individual studies. Multiple, well-done randomized clinical trials involving large numbers of patients.
Category B evidence is based on data derived from: Meta-analyses of randomized controlled trials with conflicting conclusions with regard to the directions and degrees of results between individual studies. Randomized controlled trials that involved small numbers of patients or had significant methodological flaws (e.g., bias, drop-out rate, flawed analysis, etc.). Nonrandomized studies (e.g., cohort studies, case-control studies, observational studies).
Category C evidence is based on data derived from: Expert opinion or consensus, case reports or case series.

AHFS Evidence Levels:
A - Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form (e.g., results of the introduction of penicillin treatment) to support the off-label use. Further research is unlikely to change confidence in the estimate of benefit.
B - Evidence from randomized, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate.
C - Evidence from observational studies (eg, retrospective case series/reports providing significant impact on patient care), unsystematic clinical experience, or from potentially flawed randomized, controlled trials
G - Use has been substantiated by inclusion in at least one evidence-based or consensus-based clinical practice guideline.

## Appendix 2 – Maximum daily dose for drugs of interest

HSN	GSN	Brand	Generic	Strength	Maximum Units per Day
010865	025848	PROVIGIL	MODAFINIL	100 mg	2
010865	041478	PROVIGIL	MODAFINIL	200 mg	1
034868	062819	NUVIGIL	ARMODAFINIL	150 mg	1
034868	062820	NUVIGIL	ARMODAFINIL	50 mg	5
034868	062821	NUVIGIL	ARMODAFINIL	250 mg	1
034868	072017	NUVIGIL	ARMODAFINIL	200 mg	1

## Appendix 3 – Medline literature search details

Ovid Technologies, Inc. Email Service-----Search for: limit 10 to (meta analysis or systematic reviews)Results: 27

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to June Week 2 2015> Search Strategy:

- 
- 1 modafinil.mp. (1256)
  - 2 armodafinil.mp. (99)
  - 3 1 or 2 (1281)
  - 4 exp Depression/ (82108)
  - 5 exp Fatigue/ (21739)
  - 6 exp Cognition/ (116136)
  - 7 exp Attention Deficit Disorder with Hyperactivity/ (21441)
  - 8 4 or 5 or 6 or 7 (234593)
  - 9 3 and 8 (317)
  - 10 limit 9 to (english language and humans) (284)
  - 11 limit 10 to (meta analysis or systematic reviews) (25)

\*\*\*\*\*

1. Moulton CD, Hopkins CW, Bevan-Jones WR. Systematic review of pharmacological treatments for depressive symptoms in Huntington's disease. *Mov Disord.* 2014;29(12):1556-61. doi:10.1002/mds.25980  
 AB BACKGROUND: Depressive symptoms are common in Huntington's disease (HD), profoundly affect quality of life, and predict suicidal ideation. However, no recent review of antidepressant treatment in HD has been published. METHODS: We performed a PRISMA systematic review of HD studies, which used a recognized antidepressant and measured change in depressive symptoms using a validated psychiatric scale. Controlled trials, uncontrolled trials, observational studies, and case series were included. RESULTS: Eleven studies were included, totalling 190 patients. One study examined venlafaxine, one fluoxetine, one citalopram, one atomoxetine, one modafinil, one lithium, and five antipsychotics. No studies were of adequate duration, size, or outcome, and no controlled trial in a depressed population produced a positive result. CONCLUSIONS: Inadequate evidence exists to guide antidepressant treatment in HD. Further research is needed to assess antidepressant efficacy and to examine whether treatment of depression represents a modifiable target for the high suicide rate in HD. Copyright © 2014 International Parkinson and Movement Disorder Society.

EXCLUDED; INTERVENTION

2. Bagot KS, Kaminer Y. Efficacy of stimulants for cognitive enhancement in non-attention deficit hyperactivity disorder youth: a systematic review. *Addiction.* 2014;109(4):547-57. Cited in: Ovid MEDLINE(R) at <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=24749160>. Accessed June 23, 2015.

AB BACKGROUND AND AIMS: Increasing prescription stimulant abuse among youth without diagnoses of attention deficit hyperactivity disorder (ADHD) is of concern. The most frequently cited motive for abuse is improved academic achievement via neurocognitive enhancement. Our aim in reviewing the literature was to identify neurocognitive effects of prescription stimulants in non-ADHD youth. METHODS: A systematic review

was conducted for youth aged 12-25 years using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Fourteen papers were included. RESULTS: Modafinil appears to improve reaction time ( $P < 0.04$ ), logical reasoning ( $P < 0.05$ ) and problem-solving. Methylphenidate appears to improve performance in novel tasks and attention-based tasks ( $P < 0.05$ ), and reduces planning latency in more complex tasks ( $P < 0.05$ ). Amphetamine has been shown to improve consolidation of information ( $0.02 > P < 0.05$ ), leading to improved recall. Across all three types of prescription stimulants, research shows improved attention with lack of consensus on whether these improvements are limited to simple versus complex tasks in varying youth populations. CONCLUSIONS: The heterogeneity of the non-attention deficit hyperactivity disorder youth population, the variation in cognitive task characteristics and lack of replication of studies makes assessing the potential global neurocognitive benefits of stimulants among non-attention deficit hyperactivity disorder youth difficult; however, some youth may derive benefit in specific cognitive domains.

EXCLUDED: DIAGNOSIS NOT OF INTEREST

3. Wood S, Sage JR, Shuman T, Anagnostaras SG. Psychostimulants and cognition: a continuum of behavioral and cognitive activation. *Pharmacol Rev.* 2014;66(1):193-221. doi:10.1124/pr.112.007054

AB Psychostimulants such as cocaine have been used as performance enhancers throughout recorded history. Although psychostimulants are commonly prescribed to improve attention and cognition, a great deal of literature has described their ability to induce cognitive deficits, as well as addiction. How can a single drug class be known to produce both cognitive enhancement and impairment? Properties of the particular stimulant drug itself and individual differences between users have both been suggested to dictate the outcome of stimulant use. A more parsimonious alternative, which we endorse, is that dose is the critical determining factor in cognitive effects of stimulant drugs. Herein, we review several popular stimulants (cocaine, amphetamine, methylphenidate, modafinil, and caffeine), outlining their history of use, mechanism of action, and use and abuse today. One common graphic depiction of the cognitive effects of psychostimulants is an inverted U-shaped dose-effect curve. Moderate arousal is beneficial to cognition, whereas too much activation leads to cognitive impairment. In parallel to this schematic, we propose a continuum of psychostimulant activation that covers the transition from one drug effect to another as stimulant intake is increased. Low doses of stimulants effect increased arousal, attention, and cognitive enhancement; moderate doses can lead to feelings of euphoria and power, as well as addiction and cognitive impairment; and very high doses lead to psychosis and circulatory collapse. This continuum helps account for the seemingly disparate effects of stimulant drugs, with the same drug being associated with cognitive enhancement and impairment.

EXCLUDED: DIAGNOSIS NOT OF INTEREST; NARRATIVE REVIEW

4. Sheng P, Hou L, Wang X, et al. Efficacy of modafinil on fatigue and excessive daytime sleepiness associated with neurological disorders: a systematic review and meta-analysis. *PLoS ONE.* 2013;8(12):e81802. doi:10.1371/journal.pone.0081802

AB BACKGROUND: Modafinil is a novel wake-promoting agent approved by the FDA ameliorating excessive daytime sleepiness (EDS) in three disorders: narcolepsy, shift work sleep disorder and obstructive sleep apnea. Existing trials of modafinil for fatigue and EDS associated with neurological disorders provided inconsistent results. This meta-analysis was aimed to assess drug safety and effects of modafinil on fatigue and EDS associated with neurological disorders. METHODS: A comprehensive literature review was conducted in order to identify published studies assessing the effects of modafinil on fatigue and EDS associated with neurological disorders. Primary outcomes included fatigue and EDS. Secondary outcomes included depression and adverse effects. FINDINGS: Ten randomized controlled trials were identified including 4 studies of Parkinson's disease (PD), 3 of multiple sclerosis (MS), 2 of traumatic brain injury (TBI) and 1 of post-polio syndrome (PPS). A total of 535 patients were enrolled. Our results suggested a therapeutic effect of modafinil on fatigue in TBI (MD -0.82 95% CI -1.54 - -0.11  $p=0.02$ ,  $I(2)=0\%$ ), while a beneficial effect of modafinil on fatigue was not confirmed in the pooled studies of PD or MS. Treatment results demonstrated a clear beneficial effect of modafinil on EDS in patients with PD (MD -2.45 95% CI -4.00 - -0.91  $p=0.002$   $I(2)=14\%$ ), but not with MS and TBI. No difference was seen between modafinil and placebo treatments in patients with PPS. Modafinil seemed to have no therapeutic effect on depression. Adverse events were similar between modafinil and placebo groups except that more patients were found with insomnia and nausea in modafinil group. CONCLUSIONS: Existing trials of modafinil for fatigue and EDS associated with PD, MS, TBI and PPS provided inconsistent results. The majority of the studies had small sample sizes. Modafinil is not yet sufficient to be recommended for these medical conditions until solid data are available.

INCLUDED

5. Barsevick AM, Irwin MR, Hinds P, et al. Recommendations for high-priority research on cancer-related fatigue in children and adults. *J Natl Cancer Inst.* 2013;105(19):1432-40. doi:10.1093/jnci/djt242

AB Over the past decades, some scientific progress has been made in understanding and treating cancer-related fatigue (CRF). However, three major problems have limited further progress: lack of agreement about measurement, inadequate understanding of the underlying biology, and problems in the conduct of clinical trials for CRF. This commentary reports the recommendations of a National Cancer Institute Clinical Trials Planning Meeting and an ongoing National Cancer Institute working group to address these problems so that high-priority research and clinical trials can be conducted to advance the science of CRF and its treatment. Recommendations to address measurement issues included revising the current case definition to reflect more rigorous criteria, adopting the Patient Reported Outcomes Measurement Information System fatigue scales as standard measures of CRF, and linking legacy measures to the scales. With regard to the biology of CRF, the group identified the need for longitudinal research to examine biobehavioral mechanisms underlying CRF and testing mechanistic hypotheses within the context of intervention research. To address clinical trial issues, recommendations included using only placebo-controlled trial designs, setting eligibility to minimize sample heterogeneity or enable subgroup analysis, establishing a CRF severity threshold for participation in clinical trials, conducting dissemination trials of efficacious interventions (such as exercise), and combining

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Date: September 2015

nonpharmacologic and pharmacologic interventions to exploit the potential synergy between these approaches. Accomplishing these goals has the potential to advance the science of CRF and improve the clinical management of this troubling symptom.

EXCLUDED: DESIGN (COMMENTARY)

6. Cerullo MA, Strakowski SM. A systematic review of the evidence for the treatment of acute depression in bipolar I disorder. *CNS Spectr.* 2013;18(4):199-208. doi:10.1017/S1092852913000102

AB In this article, we examined evidence for the acute treatment of depression in bipolar I disorder, focusing on double-blind, placebo-controlled studies with a definite primary outcome measure and published in peer review journals. Quetiapine and olanzapine/fluoxetine are currently approved by the FDA for the treatment of bipolar depression, and a number of additional agents (including other atypical antipsychotics, mood stabilizers, antidepressants, and novel compounds) have been studied with varying degrees of efficacy. The medication with the most evidence for efficacy in bipolar depression is quetiapine, with five studies showing positive efficacy compared to placebo. In contrast, five studies of lamotrigine were negative, although meta-analyses of the pooled have found some treatment effects. Two studies of olanzapine and olanzapine/fluoxetine and three small studies of divalproex showed significant efficacy in treating bipolar depression. Two studies of aripiprazole found no differences compared to placebo. Early research on lithium in bipolar depression had significant methodological flaws, and only one study of lithium met our primary search criteria. To better understand the role of antidepressants, we also examined studies of antidepressants as adjunctive treatment of bipolar depression in participants taking mood stabilizers or atypical antipsychotics. These studies reported mixed results for a variety of antidepressants, but the majority found no differences compared to placebo. Other studies of adjunctive treatment were also discussed. There has been one positive adjunctive study each of lamotrigine, omega-3 fatty acids, modafinil, and armodafinil, while there was one negative trial each of omega-3 fatty acids, ziprasidone, and levetiracetam.

INCLUDED

7. Scoriels L, Jones PB, Sahakian BJ. Modafinil effects on cognition and emotion in schizophrenia and its neurochemical modulation in the brain. *Neuropharmacology.* 2013;64:168-84. doi:10.1016/j.neuropharm.2012.07.011

AB Modafinil is a central nervous system wake promoting agent used for the treatment of excessive daytime sleeping. Its vigilance promoting properties and low abuse potential has intrigued the scientific community and has led to use it as a cognitive enhancer, before its neural functions were understood. Here, we review the effects of modafinil in human cognition and emotion and its specific actions on symptoms in patients with schizophrenia and whether these are consistently effective throughout the literature. We also performed a systematic review on the effects of modafinil on neurotransmitter signalling in different areas of the brain in order to better understand the neuromechanisms of its cognitive and emotional enhancing properties. A review of its effects in schizophrenia suggests that modafinil facilitates cognitive functions, with pro-mnemonic effects and problem solving improvements. Emotional processing also appears to be enhanced by the drug, although to date there are only a limited number of studies. The systematic review on the neurochemical modulation of the modafinil suggests that its mnemonic enhancing properties might be the result of glutamatergic and dopaminergic increased neuronal activation in the hippocampus and in the prefrontal cortex respectively. Other neurotransmitters were also activated by modafinil in various limbic brain areas, suggesting that the drug acts on these brain regions to influence emotional responses. These reviews seek to delineate the neuronal mechanisms by which modafinil affects cognitive and emotional function. This article is part of a Special Issue entitled 'Cognitive Enhancers'.

EXCLUDED – OUTCOMES NOT OF INTEREST

8. Kelley AM, Webb CM, Athy JR, Ley S, Gaydos S. Cognition enhancement by modafinil: a meta-analysis. *Aviat Space Environ Med.* 2012;83(7):685-90. Cited in: Ovid MEDLINE(R) at <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=22779312>. Accessed June 23, 2015.

AB INTRODUCTION: Currently, there are a number of pharmaceuticals available that have potential to enhance cognitive functioning, some of which may ultimately be considered for such use in military operations. Some drugs with potential for cognition enhancement have already been studied for use in military operations specific to their primary effect in sleep regulation (i.e., dextroamphetamine, modafinil, caffeine). There is considerable information available on many of these drugs. However, considerations for military appropriateness must be based on proficient research (e.g., randomly controlled trial design). METHODS: A meta-analysis was conducted to summarize the current state of knowledge of these potentially cognition-enhancing drugs. The analysis only included studies which met inclusion criteria relevant to military research. RESULTS: The results of the literature review reveal a gap in research of the enhancement properties of the drugs of interest. The results yielded three studies (all of which studied modafinil) that met the criteria. The meta-analysis of these three studies revealed a relatively weak pooled effect of modafinil on some aspects of cognitive performance in normal, rested adults. DISCUSSION: While the results of this study support the efficacy of modafinil, the main finding is the large literature gap evaluating the short- and long-term effects of these drugs in healthy adults.

EXCLUDED: DIAGNOSIS NOT OF INTEREST

9. Bond DJ, Hadjipavlou G, Lam RW, et al. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid attention-deficit/hyperactivity disorder. *Ann Clin Psychiatry*. 2012;24(1):23-37. Cited in: Ovid MEDLINE(R) at <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=medl&NEWS=N&AN=22303520>. Accessed June 23, 2015.

**AB BACKGROUND:** Patients with bipolar disorder (BD) and major depressive disorder (MDD) experience adult attention-deficit/hyperactivity disorder (ADHD) at rates substantially greater than the general population. Nonetheless, ADHD frequently goes untreated in this population. **METHODS:** We reviewed the literature regarding the management of adult ADHD in patients with mood disorders. Because a limited number of studies have been conducted in adults, our treatment recommendations also are partly informed by research in children and adolescents with BD+ADHD or MDD+ADHD, adults with ADHD, and our clinical experience. **RESULTS:** In individuals with mood disorders, ADHD is best diagnosed when typical symptoms persist during periods of sustained euthymia. Individuals with BD+ADHD, particularly those with bipolar I disorder (BD I), are at risk for mood destabilization with many ADHD treatments, and should be prescribed mood-stabilizing medications before initiating ADHD therapies. Bupropion is a reasonable first-line treatment for BD+ADHD, while mixed amphetamine salts and methylphenidate also may be considered in patients determined to be at low risk for manic switch. Modafinil and cognitive-behavioral therapy (CBT) are second-line choices. In patients with MDD+ADHD and moderate to severe depression, MDD should be the treatment priority, whereas in mildly depressed or euthymic patients the order may be reversed. First-line treatments for MDD+ADHD include bupropion, an antidepressant plus a long-acting stimulant, or an antidepressant plus CBT. Desipramine, nortriptyline, and venlafaxine are second-line options. **CONCLUSIONS:** Clinicians should be vigilant in screening for comorbid ADHD in mood disorder patients. ADHD symptoms can respond to appropriately chosen treatments.

**INCLUDED**

10. Kirshbaum M. Pharmacologic treatments for fatigue associated with palliative care. *Clin J Oncol Nurs*. 2011;15(4):438-9. doi:10.1188/11.CJON.438-439

**EXCLUDED:** UNAVAILABLE AT OHSU

11. Castells X, Ramos-Quiroga JA, Bosch R, Nogueira M, Casas M. Amphetamines for Attention Deficit Hyperactivity Disorder (ADHD) in adults. *Cochrane Database Syst Rev*. 2011;(6):CD007813. doi:10.1002/14651858.CD007813.pub2

**AB BACKGROUND:** Attention Deficit Hyperactivity Disorder (ADHD) is a childhood onset disorder that can persist into adulthood. Amphetamines are used to treat adult ADHD, but uncertainties persist about their efficacy and safety. **OBJECTIVES:** To examine the efficacy and safety of amphetamines for adults with ADHD, as well as the influence of dose, drug type and release formulation type. **SEARCH STRATEGY:** We searched CENTRAL, PubMed, EMBASE, CINAHL, PsycINFO, clinicaltrials.gov, UK Clinical Trials Gateway and references obtained from articles and experts in the field. We conducted the electronic searches on 25 February 2010. **SELECTION CRITERIA:** Randomized controlled trials comparing the efficacy of amphetamine derivatives against placebo or an active intervention. **DATA COLLECTION AND ANALYSIS:** Two authors extracted data from each included study. We used the standardized mean difference (SMD) and the risk ratio (RR) to assess continuous and dichotomous outcomes, respectively. We conducted a stratified analysis to determine the influence of moderating variables. We assessed the trials for risk of bias and drew a funnel plot to investigate the possibility of publication bias. **MAIN RESULTS:** We included seven studies, which enrolled 1091 participants. All studies were placebo-controlled and three included an active comparator: guanfacine, modafinil and paroxetine. Most studies had short-term follow-up, with a mean study length of 8.1 weeks. Amphetamines improved ADHD symptom severity (SMD = -0.72; 95% CI -0.87 to -0.57) but did not improve retention in treatment overall and were associated with increased dropout due to adverse events (RR 3.03; 95% CI 1.52 to 6.05). The three amphetamine derivatives investigated (dextroamphetamine, lisdexamphetamine and mixed amphetamine salts (MAS)) were all efficacious for reducing ADHD symptoms, but MAS also increased retention in treatment. Different doses did not appear associated with differences in efficacy. We investigated immediate and sustained drug release formulations but found no difference between them on any outcome. When amphetamines were compared to other drug interventions, no differences were found. We did not find any study to be at low risk of bias overall, mainly because amphetamines have powerful subjective effects that may reveal the assigned treatment. **AUTHORS' CONCLUSIONS:** Amphetamines improved short-term ADHD symptom severity. MAS also increased retention in treatment. Amphetamines were associated with higher attrition due to adverse events. The short study length and the restrictive inclusion criteria limit the external validity of these findings. Furthermore, the possibility that the results of the included studies were biased was high, which could have led to an overestimation of amphetamine efficacy.

**EXCLUDED:** INTERVENTION

12. Chamberlain SR, Robbins TW, Winder-Rhodes S, et al. Translational approaches to frontostriatal dysfunction in attention-deficit/hyperactivity disorder using a computerized neuropsychological battery. *Biol Psychiatry*. 2011;69(12):1192-203. doi:10.1016/j.biopsych.2010.08.019

**AB** Attention-deficit/hyperactivity disorder (ADHD) is a prevalent condition associated with cognitive dysfunction. The Cambridge Neuropsychological Test Automated Battery is a computerized set of tests that has been widely used in ADHD and in translation/back-translation. Following a survey of translational research relevant to ADHD in experimental animals, a comprehensive literature review was conducted of studies that had used core Cambridge Neuropsychological Test Automated Battery tests 1) to evaluate cognitive dysfunction in ADHD and 2) to evaluate effects of salient drugs in patients and in volunteers. Meta-analysis was conducted where four or more independent datasets were available. Meta-analysis revealed medium-large decrements in ADHD for response inhibition ( $d = .790, p < .001$ ), working memory ( $d = .883, p < .001$ ), executive planning ( $d = .491, p < .001$ ), and a small decrement in attentional set shifting ( $d = .160, p = .040$ ). Qualitative review of the literature showed some consistent patterns. In ADHD, methylphenidate improved working memory, modafinil

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improved planning, and methylphenidate, modafinil, and atomoxetine improved inhibition. Meta-analysis of modafinil healthy volunteer studies showed no effects on sustained attention or set shifting. Results were paralleled by findings in experimental animals on comparable tests, enabling further analysis of drug mechanisms. Substantial cognitive deficits are present in ADHD, which can be remediated somewhat with current medications and which can readily be modeled in experimental animals using back-translational methodology. The findings suggest overlapping but also distinct early cognitive effects of ADHD medications and have important implications for understanding the pathophysiology of ADHD and for future trials. Copyright © 2011 Society of Biological Psychiatry. Published by Elsevier Inc. All rights reserved.

EXCLUDED: OUTCOMES NOT OF INTEREST

13. Frost J, Okun S, Vaughan T, Heywood J, Wicks P. Patient-reported outcomes as a source of evidence in off-label prescribing: analysis of data from PatientsLikeMe. *J Med Internet Res.* 2011;13(1):e6. doi:10.2196/jmir.1643

**AB BACKGROUND:** Evaluating a new use for an existing drug can be expensive and time consuming. Providers and patients must all too often rely upon their own individual-level experience to inform clinical practice, which generates only anecdotal and unstructured data. While academic-led clinical trials are occasionally conducted to test off-label uses of drugs with expired patents, this is relatively rare. In this work, we explored how a patient-centered online research platform could supplement traditional trials to create a richer understanding of medical products postmarket by efficiently aggregating structured patient-reported data. PatientsLikeMe is a tool for patients, researchers, and caregivers (currently 82,000 members across 11 condition-based communities) that helps users make treatment decisions, manage symptoms, and improve outcomes. Members enter demographic information, longitudinal treatment, symptoms, outcome data, and treatment evaluations. These are reflected back as longitudinal health profiles and aggregated reports. Over the last 3 years, patients have entered treatment histories and evaluations on thousands of medical products. These data may aid in evaluating the effectiveness and safety of some treatments more efficiently and over a longer period of time course than is feasible through traditional trials. **OBJECTIVE:** The objective of our study was to examine the illustrative cases of amitriptyline and modafinil - drugs commonly used off-label. **METHODS:** We analyzed patient-reported treatment histories and drug evaluations for each drug, examining prevalence, treatment purpose, and evaluations of effectiveness, side effects, and burden. **RESULTS:** There were 1948 treatment histories for modafinil and 1394 treatment reports for amitriptyline reported across five PatientsLikeMe communities (multiple sclerosis, Parkinson's disease, mood conditions, fibromyalgia/chronic fatigue syndrome, and amyotrophic lateral sclerosis). In these reports, the majority of members reported taking the drug for off-label uses. Only 34 of the 1755 (1%) reporting purpose used modafinil for an approved purpose (narcolepsy or sleep apnea). Only 104 out of 1197 members (9%) reported taking amitriptyline for its approved indication, depression. Members taking amitriptyline for off-label purposes rated the drug as more effective than those who were taking it for its approved indication. While dry mouth is a commonly reported side effect of amitriptyline for most patients, 88 of 220 (40%) of people with amyotrophic lateral sclerosis on the drug reported taking advantage of this side effect to treat their symptom of excess saliva. **CONCLUSIONS:** Patient-reported outcomes, like those entered within PatientsLikeMe, offer a unique real-time approach to understand utilization and performance of treatments across many conditions. These patient-reported data can provide a new source of evidence about secondary uses and potentially identify targets for treatments to be studied systematically in traditional efficacy trials.

EXCLUDED: NOT RELEVANT

14. Peuckmann V, Elsner F, Krumm N, Trottenberg P, Radbruch L. Pharmacological treatments for fatigue associated with palliative care. *Cochrane Database Syst Rev.* 2010;(11):CD006788. doi:10.1002/14651858.CD006788.pub2

**AB BACKGROUND:** In healthy individuals, fatigue is a protective response to physical or mental stress, often relieved by rest. By contrast, in palliative care patients fatigue can be severely debilitating, thereby impacting daily activity and quality of life, often with rest not counteracting fatigue. Fatigue frequently occurs in patients with advanced disease and modalities treating cancer often contribute or cause fatigue. Further complicating issues are its multidimensionality, subjective nature, and lack of a consensus definition of fatigue. Pathophysiology is not fully understood and evidence-based treatment approaches are needed. **OBJECTIVES:** The objective was to determine efficacy of pharmacological treatments on non-specific fatigue in palliative care. The focus was on patients at an advanced stage of disease, including cancer and other chronic diseases associated with fatigue, aiming to relieve fatigue. Studies aiming at curative treatment (e.g. surgical intervention for early breast cancer) were not included. **SEARCH STRATEGY:** We searched EMBASE; Psych Lit, CENTRAL and MEDLINE to June 2009. **SELECTION CRITERIA:** We considered randomised controlled trials (RCTs) concerning adult palliative care with focus on pharmacological treatment of fatigue. The primary outcome had to be non-specific fatigue (or related terms such as asthenia). **DATA COLLECTION AND ANALYSIS:** Results were screened and included if they met the selection criteria. If two or more studies were identified that investigated a specific drug in a population with the same disease, meta-analysis was conducted. In addition, comparison of type of drug investigated in a specific population as well as comparison of frequent adverse effects of fatigue treatment was done by creating overview tables. **MAIN RESULTS:** More than 2000 publications were screened, and 22 met inclusion criteria. In total, data from 11 drugs and 1632 participants were analysed. Studies investigating amantadine, pemoline, and modafinil in participants with Multiple Sclerosis (MS)-associated fatigue and methylphenidate in patients suffering from advanced cancer and fatigue could be used for meta-analysis. Amantadine in MS and methylphenidate in cancer patients showed a superior effect. Most studies had low participant numbers and were heterogenous. **AUTHORS' CONCLUSIONS:** Based on limited evidence, we cannot recommend a specific drug for treatment of fatigue in palliative care patients. Surprisingly, corticosteroids have not been a research focus for fatigue treatment, although these drugs are frequently used. Recent fatigue research seems to focus on modafinil, which may be beneficial although there is no evidence currently. Amantadine and methylphenidate should be further examined. Consensus regarding fatigue assessment in advanced disease is needed.

## INCLUDED

15. Repantis D, Schlattmann P, Laisney O, Heuser I. Modafinil and methylphenidate for neuroenhancement in healthy individuals: A systematic review. *Pharmacol Res.* 2010;62(3):187-206. doi:10.1016/j.phrs.2010.04.002

AB The term neuroenhancement refers to improvement in the cognitive, emotional and motivational functions of healthy individuals through, inter alia, the use of drugs. Of known interventions, psychopharmacology provides readily available options, such as methylphenidate and modafinil. Both drugs are presumed to be in widespread use as cognitive enhancers for non-medical reasons. Based on a systematic review and meta-analysis we show that expectations regarding the effectiveness of these drugs exceed their actual effects, as has been demonstrated in single- or double-blind randomised controlled trials. Only studies with sufficient extractable data were included in the statistical analyses. For methylphenidate an improvement of memory was found, but no consistent evidence for other enhancing effects was uncovered. Modafinil on the other hand, was found to improve attention for well-rested individuals, while maintaining wakefulness, memory and executive functions to a significantly higher degree in sleep deprived individuals than did a placebo. However, repeated doses of modafinil were unable to prevent deterioration of cognitive performance over a longer period of sleep deprivation though maintaining wakefulness and possibly even inducing overconfidence in a person's own cognitive performance. Copyright 2010 Elsevier Ltd. All rights reserved.

## EXCLUDED: HEALTHY INDIVIDUALS

16. Jong E, Oudhoff LA, Epskamp C, et al. Predictors and treatment strategies of HIV-related fatigue in the combined antiretroviral therapy era. *AIDS.* 2010;24(10):1387-405. doi:10.1097/QAD.0b013e328339d004

AB OBJECTIVE: To assess predictors and reported treatment strategies of HIV-related fatigue in the combined antiretroviral (cART) era. METHOD: Five databases were searched and reference lists of pertinent articles were checked. Studies published since 1996 on predictors or therapy of HIV-related fatigue measured by a validated instrument were selected. RESULTS: A total of 42 studies met the inclusion criteria. The reported HIV-related fatigue prevalence in the selected studies varied from 33 to 88%. The strongest predictors for sociodemographic variables were unemployment and inadequate income. Concerning HIV-associated factors, the use of cART was the strongest predictor. Comorbidity and sleeping difficulties were important factors when assessing physiological influences. Laboratory parameters were not predictive of fatigue. The strongest and most uniform associations were observed between fatigue and psychological factors such as depression and anxiety. Reported therapeutic interventions for HIV-related fatigue include testosterone, psycho-stimulants (dextroamphetamine, methylphenidate hydrochloride, pemoline, modafinil), dehydroepiandrosterone, fluoxetine and cognitive behavioural or relaxation therapy. CONCLUSION: HIV-related fatigue has a high prevalence and is strongly associated with psychological factors such as depression and anxiety. A validated instrument should be used to measure intensity and consequences of fatigue in HIV-infected individuals. In the case of fatigue, clinicians should not only search for physical mechanisms, but should question depression and anxiety in detail. There is a need for intervention studies comparing the effect of medication (antidepressants, anxiolytics) and behavioural interventions (cognitive-behavioural therapy, relaxation therapy, graded exercise therapy) to direct the best treatment strategy. Treatment of HIV-related fatigue is important in the care for HIV-infected patients and requires a multidisciplinary approach.

## EXCLUDED: INTERVENTION

17. Brown JN, Howard CA, Kemp DW. Modafinil for the treatment of multiple sclerosis-related fatigue. *Ann Pharmacother.* 2010;44(6):1098-103. doi:10.1345/aph.1M705

AB OBJECTIVE: To review the efficacy and safety of off-label use of modafinil in the treatment of multiple sclerosis (MS)-related fatigue. DATA SOURCES: Literature was accessed via MEDLINE (1966-January 2010) and International Pharmaceutical Abstracts (1960-2010), using the medical subject heading terms modafinil, multiple sclerosis, and fatigue. STUDY SELECTION AND DATA EXTRACTION: All English-language, peer reviewed publications were analyzed for relevance. Studies appropriate to the objective were evaluated, including 3 open-label trials, 1 single-blind trial, and 2 randomized placebo-controlled trials. DATA SYNTHESIS: Fatigue symptoms, assessed by a variety of self-reported symptom scales, improved in each of the uncontrolled studies reviewed when participants with MS received modafinil 200 mg or less daily for up to 12 weeks. These benefits were not maintained, however, in one uncontrolled study when modafinil was increased to 400 mg daily. Of the 2 randomized, controlled trials, 1 study found that modafinil 200 mg once daily resulted in a reduction in fatigue symptoms measured by the Fatigue Severity Scale at 8 weeks. The other study found no difference in the reduction of fatigue symptoms, measured by the Modified Fatigue Impact Scale at 5 weeks, between the placebo group and patients who received modafinil 100-200 mg twice daily. The most common adverse reactions associated with modafinil use in all studies included gastrointestinal and central nervous system effects. CONCLUSIONS: Based on the available data, use of modafinil for the treatment of MS-related fatigue has demonstrated benefit in all uncontrolled studies but has conflicting results from 2 controlled studies. Modafinil is a reasonable therapeutic option in this patient population, although larger, long-term, randomized controlled studies are necessary to further elucidate the appropriate dose of modafinil, its effects on MS-related fatigue, and adverse effects associated with its use. [References: 26]

## INCLUDED

18. Cooper MR, Bird HM, Steinberg M. Efficacy and safety of modafinil in the treatment of cancer-related fatigue. *Ann Pharmacother.* 2009;43(4):721-5. doi:10.1345/aph.1L532

**AB OBJECTIVE:** To review the efficacy and safety of modafinil in the treatment of cancer-related fatigue (CRF). **DATA SOURCES:** Literature was accessed via MEDLINE (1950-week 3, November 2008), International Pharmaceutical Abstracts, and Google Scholar using the terms modafinil, cancer, and fatigue. Reference citations from articles identified were reviewed. **STUDY SELECTION AND DATA EXTRACTION:** All English-language publications identified were analyzed for significance. Studies relevant to the objective were used, including 2 prospective open-label studies, one randomized double-blind, dose-controlled trial with an open-label extension, and one Phase 3 randomized, placebo-controlled, double-blind trial. **DATA SYNTHESIS:** Fatigue is a nearly universal adverse effect of cancer and its treatment that is unrelated to physical exertion, is not relieved by sleep or rest, and negatively affects quality of life. Modafinil is a central nervous system stimulant with minimal toxicity and a low propensity for abuse. Clinical data demonstrate that modafinil significantly reduces fatigue in patients who have received cancer treatment or are currently undergoing chemotherapy. Additional benefits include improvement in cognitive function, mood, general activity, walking ability, normal work ability, relations with other people, and enjoyment of life. Limitations of the available data include open-label design in 3 of the 4 studies; the absence of numerical results of fatigue assessments in the abstract of 1 trial, preventing the determination of clinical significance; and the full inclusion/exclusion criteria, which were not included in the published abstracts. These limitations leave readers without a clear picture of the study populations. Finally, different patient populations at different points in treatment with varying durations of therapy were used, which makes extrapolation of data to the general population challenging. **CONCLUSIONS:** Further randomized placebo-controlled trials are necessary to amass evidence for the effective and safe use of modafinil for CRF; however, if traditional therapies have failed or are intolerable, modafinil can be considered a treatment option. [References: 19]

#### INCLUDED

19. Saavedra-Velez C, Yusim A, Anbarasan D, Lindenmayer JP. Modafinil as an adjunctive treatment of sedation, negative symptoms, and cognition in schizophrenia: a critical review. *J Clin Psychiatry.* 2009;70(1):104-12. Cited in: Ovid MEDLINE(R) at <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=19026265>. Accessed June 23, 2015.

**AB OBJECTIVE:** Given recent reports about the off-label use of modafinil as an adjuvant for the treatment of antipsychotic-associated sedation in schizophrenia patients and the recent interest in its putative cognitive-enhancing effects in this population, we present a systematic review of available data on trials of modafinil as an adjuvant in the treatment of cognitive deficits, negative symptoms, and antipsychotic-induced fatigue, and its tolerability. **DATA SOURCES:** PubMed was searched for trials published in English up to January 2008 evaluating modafinil's effects on fatigue, negative symptoms, and cognition in schizophrenia with combinations of the following terms: schizophrenia, modafinil, cognition, negative symptoms, and fatigue. **STUDY SELECTION:** Six trials were identified: 2 randomized, prospective, double-blind placebo-controlled trials; 3 randomized, prospective, double-blind placebo-controlled crossover trials; and 1 open-label pilot study. Case series and case reports were excluded in the data analysis, except to identify potential adverse reactions to modafinil. **DATA EXTRACTION:** Studies were examined for number of subjects, trial duration, design, dosing, and outcomes with respect to sedation, negative symptoms, cognitive function, and tolerability. **RESULTS:** One of 4 reviewed studies found a significant effect of modafinil as an alerting agent for antipsychotic-induced fatigue and sedation. Neither of 2 reviewed studies found modafinil to improve negative symptoms of schizophrenia. Three of 6 reviewed studies showed that modafinil may improve short-term memory, attention, and the ability to shift mental sets. Two neuroimaging studies identified functional correlates in areas associated with working memory functions. The main adverse effect was found to be a small risk of psychosis exacerbation, which was seen in 5 of 83 patients (6.0%) in the active treatment groups as compared to 2 of 70 patients (2.9%) in the placebo groups. **CONCLUSIONS:** While the available data suggest that modafinil is generally well tolerated and may have some efficacy in the treatment of antipsychotic-induced sedation and cognitive domains, the small sample sizes, contradictory results, and methodological differences between trials, especially with respect to cognitive testing, make it difficult to draw firm conclusions about the overall effectiveness of modafinil as an adjunct in the treatment of schizophrenia. Well-powered, prospective, randomized placebo-controlled trials using the MATRICS battery concomitantly with functional outcome measures are necessary to elucidate modafinil's efficacy and effectiveness as an adjunctive treatment for sedation, negative symptoms, and cognitive deficits in schizophrenia. Hence, before prescribing modafinil to a schizophrenia patient, the possible risks and benefits of each particular case should be evaluated. Copyright 2009 Physicians Postgraduate Press, Inc. [References: 56]

#### INCLUDED.

20. Harris JD. Fatigue in chronically ill patients. *Curr. opin. support. palliat. care.* 2008;2(3):180-6. doi:10.1097/SPC.0b013e32830baed0

**AB PURPOSE OF REVIEW:** Fatigue is the most common symptom among palliative patients, often considered more distressing than pain, nausea or vomiting. This article reviews the current literature and puts forward up to date treatment recommendations. **RECENT FINDINGS:** Methylphenidate showed a small but significant improvement versus placebo in a recently published systematic review. Donepezil did not show a significant benefit versus placebo in a double blind, placebo-controlled study. Hypogonadism is a frequent condition that can cause fatigue in patients with advanced cancer and other chronic illnesses and androgen replacement therapy warrants further investigation. Among antidepressants, bupropion has shown encouraging results. The role of hematopoietic agents for advanced cancer patients receiving palliative care is minimal as anemia is less of a contributing factor in this setting. Cytokine receptor antagonists play an important theoretical role but further studies are needed before they could be recommended. L-Carnitine has shown encouraging results. **SUMMARY:** Methylphenidate is still considered the first choice of treatment among pharmacological therapies. Modafinil shows promise, but insufficient studies have been conducted in this setting. Bupropion may have benefits in treating depression and fatigue. Among complementary therapies, L-carnitine has the most potential. Further studies are needed before cytokine receptor antagonists and androgen replacement therapy can be recommended. [References: 63]

#### EXCLUDED: UNAVAILABLE AT OHSU

21. Candy M, Jones L, Williams R, Tookman A, King M. Psychostimulants for depression. *Cochrane Database Syst Rev.* 2008;(2):CD006722. doi:10.1002/14651858.CD006722.pub2

**AB BACKGROUND:** Depression is common, disabling, costly and under-treated. There are problems in the current first-line drug treatment, antidepressants, for moderate or severe depression. There is a body of research that has evaluated the effect of psychostimulants (PS) in the treatment of depression. This has not been reviewed systematically. **OBJECTIVES:** To determine the effectiveness of PS in the treatment of depression and to assess adverse events associated with PS. **SEARCH STRATEGY:** Databases CCDANCTR-Studies and CCDANCTR-References were searched on 21/6/2006. Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, PsycInfo, AMED, CINAHL, Dissertation Abstracts and the National Health Service Research Register were searched. **SELECTION CRITERIA:** Randomised controlled trials (RCTs) assessing the effectiveness of PS were included. The trial population comprised adults of either sex with a diagnosis of depression. **DATA COLLECTION AND ANALYSIS:** Two review authors extracted the data independently and assessed trial quality. Meta-analysis was considered for trials with comparable key characteristics. The primary outcome was depression symptoms, based on a continuous outcome, using the standardised mean difference (SMD), or a dichotomous measure of clinical response, using odds ratios (OR), with 95% confidence intervals (CI). **MAIN RESULTS:** Twenty-four RCTs were identified. The overall quality of the trials was low. Five drugs were evaluated; dexamphetamine, methylphenidate, methylamphetamine, pemoline and modafinil. Modafinil was evaluated separately as its pharmacology is different to that of the other PS. PS were administered as a monotherapy, adjunct therapy, in oral or intravenous preparation and in comparison with a placebo or an active therapy. Most effects were measured in the short term (up to four weeks). Thirteen trials had some usable data for meta-analyses. Three trials (62 participants) demonstrated that oral PS, as a monotherapy, significantly reduced short term depressive symptoms in comparison with placebo (SMD -0.87, 95% CI -1.40, -0.33, with non-significant heterogeneity. A similar effect was found for fatigue. In the short term PS were acceptable and well tolerated. Tolerance and dependence were under evaluated. No statistically significant difference in depression symptoms was found between modafinil and placebo. **AUTHORS' CONCLUSIONS:** There is some evidence that in the short-term, PS reduce symptoms of depression. Whilst this reduction is statistically significant, the clinical significance is less clear. Larger high quality trials with longer follow-up and evaluation of tolerance and dependence are needed to test the robustness of these findings and, furthermore, to explore which PS may be more beneficial and in which clinical situations they are optimal. [References: 126]

#### INCLUDED

22. Carroll JK, Kohli S, Mustian KM, Roscoe JA, Morrow GR. Pharmacologic treatment of cancer-related fatigue. *Oncologist.* 2007;12 Suppl 1:43-51. Cited in: Ovid MEDLINE(R) at <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=17573455>. Accessed June 23, 2015.

AB Fatigue is the most commonly reported symptom in patients with cancer, with a prevalence of over 60% reported in the majority of studies. This paper systematically reviews pharmacologic agents in the treatment of cancer-related fatigue (CRF). We conducted a literature review of clinical trials that assessed pharmacologic agents for the treatment of CRF. These agents include hematopoietics (for anemia), corticosteroids, and psychostimulants. Other therapeutic agents that are less well studied for CRF but are currently the focus of clinical trials include l-carnitine, modafinil, bupropion, and selective serotonin reuptake inhibitors such as paroxetine. Disclosure of potential conflicts of interest is found at the end of this article. [References: 75]

#### EXCLUDED: UNAVAILABLE AT OHSU

23. Lam JY, Freeman MK, Cates ME. Modafinil augmentation for residual symptoms of fatigue in patients with a partial response to antidepressants. *Ann Pharmacother.* 2007;41(6):1005-12. Cited in: Ovid MEDLINE(R) at <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=17519297>. Accessed June 23, 2015.

**AB OBJECTIVE:** To evaluate the literature discussing the use of modafinil in the treatment of residual symptoms of fatigue in patients with depression. **DATA SOURCES:** PubMed (1966-March 2007) and International Pharmaceutical Abstracts (1970-March 2007) were searched using the key words modafinil and depression. A manual search of the reference section of the articles retrieved was conducted to identify articles not indexed in either of these sources. **STUDY SELECTION AND DATA EXTRACTION:** All articles published in English were evaluated. Studies were included if modafinil was used to treat patients with residual fatigue from depression and the effects were measured with validated fatigue subscales. **DATA SYNTHESIS:** One retrospective study, 5 open-label trials, and 2 randomized controlled clinical trials met the inclusion criteria for assessment of residual symptoms of fatigue as assessed by commonly used fatigue subscales after modafinil administration. Although improvement with fatigue has occurred with modafinil therapy, literature regarding the topic is limited by the lack of well-controlled clinical trials. Modafinil does appear to improve residual fatigue with depression as evidenced by open-label trials; however, the efficacy of this agent has not been duplicated in randomized controlled trials. The open-label trials that have been conducted often had no comparator and a small number of patients. In addition, outcome measures used in the studies were not consistent between trials. Modafinil appears to be well tolerated, with the main adverse effects being headache and nausea. **CONCLUSIONS:** Open-label trials indicate that modafinil may be effective in ameliorating fatigue associated with depression; however, this effect has not been reproduced in randomized, double-blind, placebo-controlled clinical trials. Therefore, the use of modafinil for the treatment of residual fatigue is not recommended due to the lack of reproducible data of its efficacy. Long-term, adequately powered clinical trials should be conducted to determine its place in therapy. [References: 24]

#### INCLUDED

24. Lindsay SE, Gudelsky GA, Heaton PC. Use of modafinil for the treatment of attention deficit/hyperactivity disorder. *Ann Pharmacother.* 2006;40(10):1829-33. Cited in: Ovid MEDLINE(R) at <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=16954326>. Accessed June 23, 2015.

Author: Ketchum

Date: September 2015

AB OBJECTIVE: To review the evidence for the use of modafinil in the treatment of attention deficit/hyperactivity disorder (ADHD). DATA SOURCES: A MEDLINE search (January 1990-May 2006) was conducted using MeSH terms ADHD and modafinil. The search was limited to English-language articles on clinical trials in humans. The Cochrane Database was also searched. STUDY SELECTION AND DATA EXTRACTION: The literature search yielded 4 randomized clinical trials. DATA SYNTHESIS: The use of modafinil in the treatment of ADHD is associated with significant improvements in primary outcome measures used to assess the status of patients diagnosed with ADHD. Several aspects of cognitive function in ADHD patients also appear to improve following modafinil treatment. Modafinil shows a favorable adverse effect profile. Insomnia and headache were the most common adverse effects, seen in approximately 20% of treated individuals. However, it has not been demonstrated that the beneficial effects of modafinil are maintained with chronic administration. CONCLUSIONS: Modafinil may be a viable option for some patients in the treatment of ADHD, perhaps those for whom standard ADHD therapies have not been successful or tolerated. There remains a need for additional large, long-term studies using flexible titration methods to optimize the dose of modafinil to establish safety and efficacy, as well as head-to-head comparisons between modafinil and both long- and short-acting stimulants to determine the role of modafinil in the treatment of ADHD. [References: 13]

#### INCLUDED

25. Ballon JS, Feifel D. A systematic review of modafinil: Potential clinical uses and mechanisms of action. *J Clin Psychiatry.* 2006;67(4):554-66. Cited in: Ovid MEDLINE(R) at <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=16669720>. Accessed June 23, 2015.

AB BACKGROUND: Modafinil is a novel wake-promoting agent that has U.S. Food and Drug Administration approval for narcolepsy and shift work sleep disorder and as adjunctive treatment of obstructive sleep apnea/hypopnea syndrome. Modafinil has a novel mechanism and is theorized to work in a localized manner, utilizing hypocretin, histamine, epinephrine, gamma-aminobutyric acid, and glutamate. It is a well-tolerated medication with low propensity for abuse and is frequently used for off-label indications. The objective of this study was to systematically review the available evidence supporting the clinical use of modafinil. DATA SOURCES: The search term modafinil OR Provigil was searched on PubMed. Selected articles were mined for further potential sources of data. Abstracts from major scientific conferences were reviewed. Lastly, the manufacturer of modafinil in the United States was asked to provide all publications, abstracts, and unpublished data regarding studies of modafinil. DATA SYNTHESIS: There have been 33 double-blind, placebo-controlled trials of modafinil. Additionally, numerous smaller studies have been performed, and case reports of modafinil's use abound in the literature. CONCLUSIONS: Modafinil is a promising drug with a large potential for many uses in psychiatry and general medicine. Treating daytime sleepiness is complex, and determining the precise nature of the sleep disorder is vital. Modafinil may be an effective agent in many sleep conditions. To date, the strongest evidence among off-label uses exists for the use of modafinil in attention-deficit disorder, postanesthetic sedation, and cocaine dependence and withdrawal and as an adjunct to antidepressants for depression. [References: 146]

#### EXCLUDED: OUTCOMES

Appendix 4. Proposed Prior Authorization Criteria.

**Modafinil / Armodafinil**

**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 (ICD10 G47411; G47419; G4730; G4731; G4733; G4739)

**Covered Alternatives:**

- Preferred alternatives listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

**Table 1. Funded Indications.**

<b>Indication</b>	<b>Modafinil (Provigil™)</b>	<b>Armodafinil (Nuvigil™)</b>
Excessive daytime sleepiness in narcolepsy	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older
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)	Not FDA approved; Low level evidence of inconsistent benefit	Not FDA approved; insufficient evidence
Cancer-related fatigue	Not FDA approved; Low level evidence of inconsistent benefit	Not FDA approved; insufficient evidence
Multiple sclerosis-related fatigue	Not FDA approved; Low level evidence of inconsistent benefit	Not FDA approved; insufficient evidence

Drug-related fatigue	Not FDA approved; insufficient evidence	Not FDA approved;
Excessive daytime sleepiness or fatigue related to other neurological disorders (e.g. Parkinson's Disease, traumatic brain injury, post-polio syndrome)	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence
ADHD	Not FDA approved; Insufficient evidence	Not FDA approved; insufficient evidence
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 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 this a funded diagnosis?  Non-funded diagnoses: - Shift work disorder (ICD10 G4720-4729; G4750-4769; G478) - Unspecified hypersomnia (ICD10 G4710)	Yes: Go to #3	No: Pass to RPh; Deny, not funded by OHP
3. Will prescriber consider a preferred alternative?	Yes: Inform prescriber of options (eg, preferred methylphenidate)	No: Go to #4

Approval Criteria		
4. Is the request for continuation of current therapy?	Yes: Pass to RPh; Go to #12	No: Go to #5
5. Is the prescribed daily dose higher than recommended in Table 2?	Yes: Pass to RPh; Deny for medical appropriateness.	No: Go to #6
6. Is diagnosis narcolepsy or obstructive sleep apnea (ICD10 G47411; G47419; G4730; G4731; G4733; G4739) AND is the drug prescribed by, or in consultation with, a sleep specialist or neurologist?	Yes: Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	No: Go to #7
7. Is the request for armodafinil?	Yes: Pass to RPh; Deny for medical appropriateness.  There is insufficient evidence for any off-label use.	No: Go to #8
8. Is the diagnosis unipolar or bipolar depression?	Yes: Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	No: Go to #9
9. Is the diagnosis 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.	No: Go to #10
10. Is the diagnosis ADHD?	Yes: Pass to RPh; Deny for medical appropriateness.  There is insufficient evidence for benefit for ADHD. See available options at <a href="http://www.orpdl.org/drugs/">www.orpdl.org/drugs/</a>	No: Go to #11

## Approval Criteria

11. All other diagnoses must be evaluated as to the OHP-funding level and evidence for clinical benefit.

- Evidence supporting treatment for excessive daytime sleepiness 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.

12. Continuation of therapy requires submission of documented evidence of clinical benefit and tolerability (faxed copy or equivalent). The same clinical measure (eg, Epworth score, Brief Fatigue Inventory, or other validated measure) used to diagnose fatigue or depression is recommended to document clinical benefit.

- Approve up to 12 months with chart documentation of positive response.
- Deny for “medical appropriateness” in absence of documented benefit.

*P&T / DUR Review:* 09/15 (kk)  
*Implementation:* TBD