Reviews/Evaluations

The Off-Label Use of Modafinil

Modafinil (Provigil) is a medication used to promote wakefulness. Originally marketed in 1998, modafinil, a Schedule C-IV drug, was approved by the Food and Drug Administration (FDA) for the treatment of excessive sleepiness (ES) associated with narcolepsy. In 2003, the FDA approved modafinil for the treatment of ES associated with obstructive sleep apnea-hypopnea syndrome (only as an adjunct to standard treatment) and shift work sleep disorder. With the addition of the later two indications, the potential treatment population increased from 135,000 Americans with narcolepsy to 12 million American with sleep apnea and approximate 4 million night shift workers with shift work sleep disorder.[1] Recently, a number of case reports, open label studies, and a small number of randomized trials have been published that evaluate the use of modafinil for off-label indications. A brief drug utilization review and literature evaluation follow.

Utilization of Modafinil in Oregon Fee-For-Service Patients

The use of modafinil in the State of Oregon has steadily increased since its release in 1998. Between January 1, 2002 and June 1, 2004 the volume of modafinil prescriptions dispensed increased from 3.3/10,000 to 8.0/10,000 members/month (Figure 1). This represents a 137% increase. The ingredient costs PMPM also increased from $0.06 to $0.18 (a 205% increase) during the same time period (Figure 2).

Figure 1: Rx Volume Per 10,000 Members

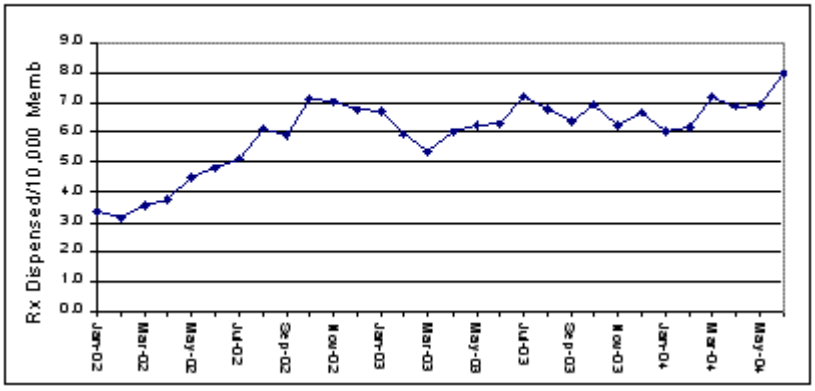
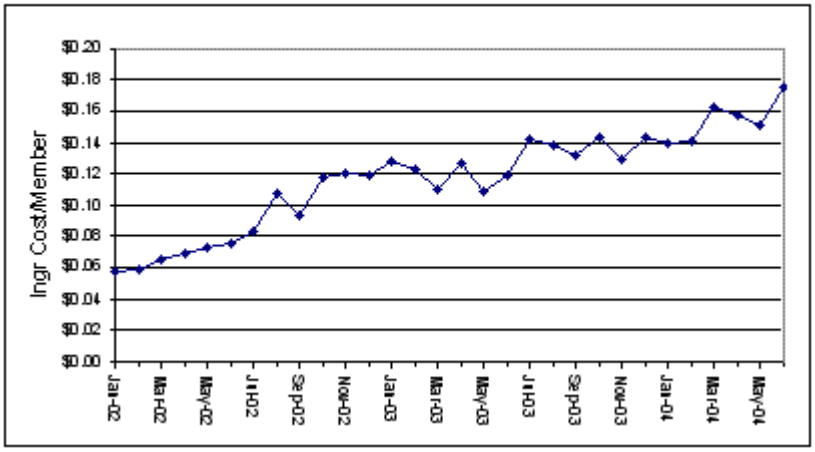


Figure 2: Ingredient Cost Per Member



In the last 12 months (July 2003 – June 2004), modafinil accounted for $661,103 ($55,092/month) in expenditures for the OHP. The average cost per prescription during this period was $216. The average cost per prescription in January 2002 was $172 (~28% increase from January 2002 to June 2004).

Patient Characteristics

Modafinil is a class 11 medication, and as such it is carved out from all OHP fully capitated health plans (FCHP). During 2003, 624 unique patients received a prescription for modafinil. Of this group, 280 had FCHP enrollment during the evaluation period. The patient characteristics are shown in table 1 below.

Table 1: Modafinil User Characteristics

Plan	N	PCT	Average Age (SD)	Age Range	N female	PCT female
FFS	344	55.1%	47.0 (15.4)	6-96	230	66.9%
FCHP	280	44.9%	42.5 (15.1)	10-92	179	63.9%
Total	624	45.0 (15.4)		6-96	409	65.5%

Of the 344 FFS clients with no FCHP enrollment during the study period, 49 (14.2%) did not have any diagnoses recorded within the medical claims. Table 2 below shows the number and percentage of unique patients with selected relevant diagnoses. Multiple sclerosis (ICD-9 code 340) was the diagnosis most frequently encountered overall. Only a negligible number of patients (n=4) had a diagnosis of attention deficit hyperactivity disorder.

Table 2: Percentage of Patients with Selected Diagnoses

Diagnosis	Unique Patients (n=344)	PCT
MULTIPLE SCLEROSIS	67	19.5%
MALAISE AND FATIGUE NEC	41	11.9%
DEPRESSIVE DISORDER NEC	28	8.1%
HYPERSOMNI W SLEEP APNEA	27	7.8%
CATAPLEXY AND NARCOLEPSY	13	3.8%

Prescriber Characteristics

Prescriber characteristics were evaluated by tabulating unique members (n=624) who had a prescription for modafinil by unique prescriber type or specialty. Because over the course of the year, a client could have had the drug prescribed by more than one provider or billed by the pharmacist to more than one provider (or a provider and the default code) the total unique patient prescriber combinations is greater than number of patients. Next to the default billing code, neurologists were the most frequent prescriber of this drug (98 unique patients, 15.7 % of total), followed by internal medicine (91, 14.6%), family practice (90, 14.4%), and psychiatry (78, 12.5%). Table 3 shows the provider characteristics and the number and percentage of unique members with a prescription for modafinil.

Table 3: Prescriber Characteristics

Prescriber Type/Specialty	Count	PCT (count/624)
OMAP default (unknowns)	231	37.0%
Neurology	98	15.7%
Internal medicine	91	14.6%
Family practice	90	14.4%

Psychiatry	78	12.5%
Hospital	41	6.6%
Nurse practitioner	39	6.3%
Mental Health Clinic	36	5.8%
Anesthesiology	17	2.7%
Pediatrics	11	1.8%
Physical/Rehab med	6	1.0%
Child Neurology	5	0.8%
Other	40	6.4%

The Off-Label Use of Modafinil

Based on the utilization review of Oregon fee-for-service drug claims data, there appears to be a developing pattern of modafinil use that is not approved by the FDA. Modafinil has been used to treat fatigue associated with Multiple Sclerosis, as an adjunct for the treatment of major depressive disorder (MDD), as a treatment for the adverse effects caused by sedating medications and has been reported to be used as a substitute for traditional stimulant therapy in attention deficit/hyperactivity disorder (ADHD). The following literature review will discuss the published studies that have evaluated the use of modafinil for off-label indications.

Fatigue Associated with Multiple Sclerosis

Fatigue is the most common symptom reported by patients diagnosed with multiple sclerosis (MS). The syndrome of fatigue is characterized by uncontrollable apathy, exhaustion, fatigability and lack of energy. A number of drugs have been investigated for the management of MS-associated fatigue syndrome including amantadine, pemoline, aminopyridines, antidepressants, and modafinil.

Rammohan et al. conducted one of the first studies evaluating the use of modafinil in MS-related fatigue.[2] Patients were treated with two weeks of placebo, two weeks of 200mg/d modafinil, and two weeks of 400mg/d modafinil. The authors found that with the dose of 200mg/d patients showed a significant improvement in fatigue compared with the placebo run in. Interestingly, this improvement compared to placebo was not demonstrated with the 400mg/d dose. This finding could be perceived two ways: 1) the 400mg/d dose is not as effective as the lower 200mg/d dose, or 2) similar to the depression studies, modafinil is maximally effective in the first two weeks of treatment. The authors speculate that the higher dose was associated with more side effects that may have masked the benefit.

As a follow-up to this study, Zifko et al. conducted an open label study to establish the efficacy, safety and appropriate dose of modafinil in the treatment of fatigue and sleepiness in patients with MS.[3] Anecdotally, the authors report statistically significant improvement in fatigue measures at the end of three months. The average dose of modafinil in patients who experienced improvement and fewer side effects was relatively low.

Key Findings:

- There are no published double-blind, randomized controlled trials of modafinil in MS-associated fatigue.
- Currently available data suggests that modafanil should be used at lower doses.

Depression

Despite the lack of good evidence, stimulant medications are sometimes used as adjuncts in the treatment of major depressive disorder (MDD). Treatment guidelines do not promote the use of polypharmacy, however, without an adequate trial of antidepressant monotherapy.[4] For those patients who are considered partial responders after 4 to 6 weeks of therapeutically dosed

antidepressant treatment, the American Psychiatric Association recommends lithium, thyroid hormone, certain anticonvulsants or psychostimulants as possible adjuncts. Stimulants, including modafinil, may be useful at treating hypersomnolence, a symptom usually associated with atypical depression. Both MDD and the frequently used antidepressants are typically associated with insomnia, a factor that could be negatively influenced by the addition of modafinil therapy.

In the only randomized, placebo-controlled study of modafinil for the adjunctive treatment of MDD, the authors concluded that modafinil may be a useful adjunct for the short-term management of residual fatigue and sleepiness in antidepressant partial responders.[5] Upon further investigation, however, the results of this study were not promising. At study end, there were no statistically significant differences between modafinil and placebo in any of the outcome measures. For certain measures, there were significant differences between the two groups at weeks one and two. These findings led the authors to recommend the use of adjunctive modafinil on strictly a short-term basis.

These findings were mirrored in an open-label study conducted by DeBattista et al published earlier this year.[6] In this study, 31 patients were given modafinil as adjunctive treatment after only 4 weeks of antidepressant therapy. Their findings indicated that statistically significant improvement in outcomes measures occurred within the first two weeks of therapy. While these improvements were maintained, no further improvements were noted. This data leads one to question whether these patients would have improved on antidepressant alone given that the patients were given a relatively short trial of monotherapy before being classified as partial responders.

In a 6-week open label study, Ninan and colleagues evaluated the use of fixed-dose modafinil in combination with either fluoxetine or paroxetine at fixed doses.[7] To be included, patients had to be diagnosed with MDD and off antidepressant medications for 4 weeks. In their evaluation, the authors found that the combination of a selective serotonin reuptake inhibitor (SSRI) and modafinil significant improved measures of depression and fatigue when compared to baseline. Without a control group, this study design fails to demonstrate how these improvements differ from antidepressant alone.

Key Findings:

- There is only one published randomized, double-blind, placebo controlled study looking at the adjunctive use of modafinil in the treatment of depression.
- Modafinil appears to be equivalent to placebo when looking at measures of depression and fatigue after two weeks of treatment.

Drug-Induced Sleepiness

A number of small-scale studies or case reports have been published evaluating the use of modafinil for drug-induced sleepiness. Drugs such as antipsychotics, narcotics, and sedative/hypnotics can cause daytime sleepiness. Currently, there are no well-supported studies that recommend this off-label use of modafinil.

Attention Deficit/Hyperactivity Disorder

A small number of studies have evaluated the use of modafinil for the treatment of ADHD in children. Even fewer published trials are available for adults. Modafinil is a stimulant medication. Although its mechanism of action is not completely understood, modafinil appears to alter the balance of gamma aminobutyric acid (GABA) and glutamate, resulting in the activation of the hypothalamus. Because modafinil has a longer half-life (15 hours) than some of the traditional stimulant medications, prescribers may hope to use modafinil as a once-a-day treatment for ADHD. According to the manufacturer, however “Provigil is not indicated for the management of symptoms associated with ADHD.”[8]

Rugino and Copley completed an open-label study evaluating the use of once daily modafinil in children age 5 to 15 years.[9] Of the 15 subjects enrolled, only 11 had data for inclusion in the study

results. The mean dose of modafinil was 195mg daily (range 50-400mg) taken for an average of 4.6 weeks (range 2-7 weeks). Primary outcome measures included the Test of Variables of Attention (TOVA), the ADHD Rating Scale-IV, and the Conners Parent and Teacher Rating Scale-Revised (CPRS, CTRS). Without a comparator, the results of this study are harder to interpret. While scores on the TOVA impulsivity subscale appeared to improve, those for the TOVA inattention subscale did not. Modest improvements were also noted in the ADHD Rating Scale-IV (88th percentile ?11.4 to the 75 percentile ?15.4) and the CPRS (82.1?7.96 to 64.4?9.18) and CTRS (77.9?9.26 to 63.8?13.2). With a small sample size (n=11), no control group, and the use of nonblinded ratings, this open-label study does not provide significant evidence for the use of modafinil in ADHD.

The same author did a follow-up study to test the hypothesis that modafinil may improve the clinical features of children with ADHD. Subsequently, Rugino and Samsock[10] evaluated the use of modafinil 100-400mg daily in 22 children aged 5-15 years in a randomized, placebo-controlled study. The authors found statistically significant improvements in TOVA scores, DSM-IV symptoms, and Conners ADHD scales. There was no statistically significant difference in ADHD Rating Scales, however. This study had an extremely short duration of only 5 days at a steady treatment dose. Further evaluation of modafinil using a similar study design with a larger population and longer duration of action will be more useful in determining the impact that this drug will have on the treatment of ADHD.

In the single manufacturer-sponsored study of modafinil in the treatment of ADHD, Cephalon studied the effectiveness of their drug in the treatment of 113 adult patients with ADHD. In this double-blind, placebo controlled study, there were no significant differences between treatment with modafinil (100 or 400mg/day) and placebo as measured by the DSM IV ADHD rating scale.[8]

Taylor and Russo[11] conducted a small three-phase crossover study of adult patients (n=21) with ADHD comparing placebo, modafinil and dextroamphetamine. Both active treatments showed significant improvement in the DSM-IV ADHD checklist when compared to placebo. All other measures failed to show statistical significance.

A comparison of the published studies identifies the following common adverse effects associated with modafinil treatment: delayed sleep onset, gastrointestinal complaints, and headache. Other medication related side effects were lightheadedness, tremors, and disorientation. In many cases, the adverse effects resolved either spontaneously or with dose reduction.

Key Findings:

- In the only large-scale study reviewing the use of modafinil in adult ADHD, there were no statistically significant improvements in ADHD scores over placebo.
- Additional studies comparing modafinil to placebo or other active treatments are required before recommendations for the use of modafinil in ADHD can be made.

Summary of Key Findings and Recommendations for Further Study

Modafinil is an expensive medication with a limited number of FDA-approved indications. Its use as a stimulant and wake-promoting agent in off-label indications is rapidly expanding without a supportive body of evidence. Based on a preliminary drug utilization review of modafinil in Oregon Medicaid pharmacy claims, it is recommended that a more thorough evaluation of the utilization of this drug be conducted. Specific areas of study would include: indication, concurrent medications, dose, duration, prescriber type, and documentation of effectiveness.

Table 4. Summary of Clinically Significant Modafinil Studies for Off-Label Indications

Study	Treatment	Population	Results	Reference
ADHD—Children				

Rugino TA, Copley TC 8/99-1/00 Open-label 2 week duration once dose was stable	100-400mg QAM	N=15 Children age 5-15 years 9M, 6F	Difference in TOVA inattention subscale 0.621 (p=.086), TOVA impulsivity subscale 1.02 (p=.006), ADHD Rating Scale-IV –13.0 (p=.047), CPRS –17.7 (p=.001), CTRS –14.1 (p=.0009)	J Am Acad Child Adolesc Psychiatry. 2001, 40(2):230-35.
Rugino TA, Samsock TC R, DB, P-C Duration=5 days at stable dose	100-400mg QAM Flexible dose titrated to effect	N=22 (11-tx, 11-control) Children age 5-15 years 15M, 9F	TOVA ADHD z similar to placebo. ADHD Rating Scale-IV (88th percentile ±11.4 to the 75 percentile ±15.4) , CPRS (82.1±7.96 to 64.4±9.18) , CTRS (77.9±9.26 to 63.8±13.2	Pediatr Neurol. 2003;29():136-142.
Cephalon DB, PC Duration=unknown	100mg or 400mg QD	N=113 adults	No difference from placebo on ADHD rating scale.	Manufacturer correspondence
Taylor FB, Russo J DB, PC, crossover Duration = 6 weeks, 2 weeks/treatment phase	100-400mg daily Modafinil mean dose = 207mg Dextroamphetamine mean dose = 22mg	N=22 Adults aged 18-59	Significant improvement on DSM-IV ADHD checklist. No improvement in COWAT, Stroop, or Digit Span.	J Child Adolesc Psychopharmacol. 2000;10(4):311-320.
Depression				
DeBattista C, Doghramji K, Menza MA, et al. R, DB, PC Duration = 6 weeks	100-400mg daily	N=118 Adults aged 18-65 years	At 6 weeks, no statistically significant differences in FSS, ESS, HAM-D, CGI-C, SF-36	J Clin Psychiatry. 2003;64(9):1057-1064.
DeBattista C, Lembke A, Solvason B, et al. Open-label Duration = 4 weeks	100-400mg daily (Average dose = 276mg)	N=31 Adults aged 26-72 13M, 18F	Change from baseline to 2 weeks statistically significant differences in HDRS, BDI, VASF, FSI, CGIS. Between 2 and 4 weeks, no statistically significant differences in same measures. Only one of four neurocognitive test showed a significant difference from baseline to week 4.	J Clin Psychopharmacol. 2004;24(1):87-90
Ninan PT, Hassman HA, Glass SJ, McManus FC. Open-label Duration = 6 weeks	200mg daily in combination with paroxetine or fluoxetine 20mg/d.	N=29 Adults aged 18-65 years	Statistically significant reductions from baseline were seen at weeks 1 through 6 on SIGH-D, HAM-D, FSS, ESS	J Clin Psychiatry. 2004;65(3):414-420.
MS-Related Fatigue				
Rammohan KW, Rosenberg JH, Lynn DJ, et al. SB, PC, crossover Duration = 9 weeks	Placebo wks 2&3 200mg/d wks 3&4 400mg/d wks 5&6	N=72 Adults aged 18-65 18M, 54F	Compared to placebo 200mg dose statistically significantly improved ESS and FSS scores. At 400mg, improvement in ESS only.	J Neurol Neurosurg Psychiatry. 2002;72():179-183.
Zifko UA, Rupp M, Schwarz S, et al. Open label Duration = 3 months	100-300mg daily Mean dose = 148mg/d	N=50 Adults aged 30-51 20M, 30F	Statistically significant improvement from baseline in FSS and ESS at doses from 100-300mg/d.	J Neurol. 2002;249():983-987.

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