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Off-Label Use of Modafinil (Provigil®)

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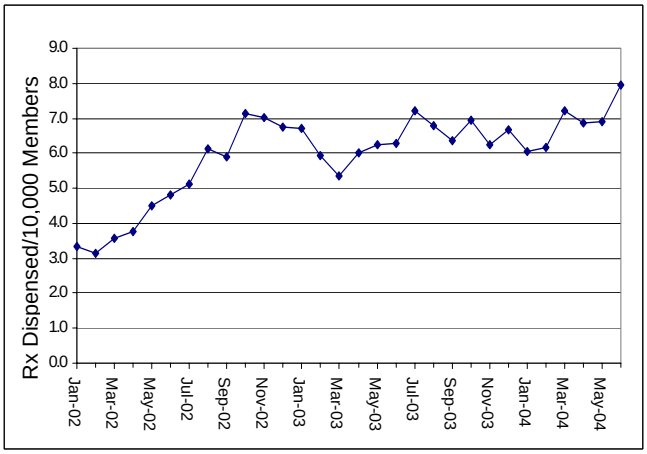
Modafinil (Provigil®) is a medication used to promote wakefulness. Originally marketed in 1998, modafinil, a Schedule C-IV drug, was approved by the Food and Drug Administration (FDA) for the treatment of excessive sleepiness (ES) associated with narcolepsy. In 2003, the FDA approved modafinil for the 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]

Modafinil is an expensive medication with an average cost per prescription of $216. The use of modafinil in the Oregon Health Plan (OHP) 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. This represents a 137% increase. (Figure 1).

Figure 1: Rx Volume Per 10,000 Members



The use of modafinil has not been limited to FDA-approved uses. In 2003, there were 344 unique fee-for-service OHP recipients who had at least one claim for modafinil. Table 1 shows that only 4% of patients taking modafinil had a known diagnosis of narcolepsy, and only 8% had a diagnosis of sleep apnea and 14% had no diagnostic claims at all. Patients included in this evaluation may have more than one of the listed diagnoses. For many of the 344 patients, modafinil was co-administered with another medication. Sixty-five percent of patients were also taking an antidepressant, 5% were receiving another stimulant, and 36% were receiving a sedative/hypnotic.

Table 1. Percentage of Patients with Selected Diagnoses

Diagnosis	Unique Patients (n=344)	PCT
Multiple Sclerosis	67	19.5%
Malaise and Fatigue	41	11.9%
Major Depressive Disorder	28	8.1%
Hypersomnia with Sleep Apnea	27	7.8%
Cataplexy and Narcolepsy	13	3.8%

Recently, 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 summary of the published open-label and randomized studies is available in Table 2.

Table 2. Summary of Significant Modafinil Studies for Off-Label Indications

Study	Treatment	Population	Results
Attention Deficit/Hyperactivity Disorder			
Rugino TA, Copley TC[9] Open-label Duration= 2 weeks, at stable dose	100-400mg QAM	N=15 Age=5-15 9M, 6F	Difference in TOVA inattention subscale: 0.621 (p=.086) TOVA impulsivity subscale: 1.02 (p=.006) DSM-IV ADHD Rating Scale-:–13.0 (p=.047) CPRS: –17.7 (p=.001) CTRS: –14.1 (p=.0009)
Rugino TA, Samsock TC[10] R, DB, PC Duration=5 days at stable dose	100-400mg QAM (titrated to effect)	N=22 Age=5-15 15M, 9F	TOVA ADHD: similar to placebo DSM-IV ADHD Rating Scale: Mod = 88th percentile ±11.4 P= 75th percentile ±15.4 CPRS: Mod = 82.1±7.96 P= 64.4±9.18 CTRS: Mod =77.9±9.26 P=63.8±13.2
Cephalon[8] DB, PC Duration=unknown	100mg or 400mg QD	N=113 Adults	DSM-IV ADHD Rating Scale: No difference
Taylor FB, Russo J[11] DB, PC, crossover Duration = 6 weeks, 2 weeks / treatment phase	Mod: mean dose = 207mg Dex: mean dose = 22mg	N=21 Age=18-59	Mod or Dex vs. Placebo : DSM-IV ADHD checklist: Improved COWAT, Stroop, and Digit Span: Not improved
Depression			
DeBattista C, Doghramji K, Menza MA, et al.[5] R, DB, PC Duration = 6 weeks	100-400mg QD	N=118 Age= 18-65	No differences in FSS, ESS, HAM-D, CGI-C, SF-36
DeBattista C, Lembke A, Solvason B, et al.[6] Open-label Duration = 4 weeks	100 -400mg QD mean dose = 276mg	N=31 Age=26-72 13M, 18F	Change from baseline to 2 weeks: differences in HDRS, BDI, VASF, FSI, CGIS. Between 2 and 4 weeks: no differences in same measures
Ninan PT, Hassman HA, Glass SJ, McManus FC.[7] Open-label Duration = 6 weeks	200mg QD + SSRI QD	N=29 Age=18-65	Reductions from baseline were seen at weeks 1 through 6 on SIGH-D, HAM-D, FSS, ESS
Multiple Sclerosis-Related Fatigue			
Rammohan KW, Rosenberg JH, Lynn DJ, et al. [2] SB, PC, crossover Duration = 9 weeks	Week 2 & 3 = Placebo Week 3 & 4 = 200mg Week 5 & 6 = 400mg	N=72 Age=18-65 18M, 54F	Placebo vs. Mod 200mg : improved ESS & FSS scores. Placebo vs. Mod 400mg: improved ESS only
Zifko UA, Rupp M, Schwarz S, et al.[3] Open label Duration = 3 months	100-300mg QD mean dose = 148mg	N=50 Age=30-51 20M,30F	Improvement from baseline in FSS and ESS at all doses.

PC=Placebo-Controlled; R=Randomized; DB=Double-Blind; SB=Single-Blind; Mod=modafinil; Dex=dextroamphetamine; TOVA= Test of Variables of Attention, CPRS, CTRS=Conners Parent and Teacher, Rating Scale-Revised, COWAT=Controlled Oral Word Association Test, FSS=Fatigue Severity Scale, ESS=Epworth Sleepiness Scale, HAM-D, HDRS=Hamilton Rating Scale for Depression, CGI-C=Clinical Global Impression of Change, SF-36=Medical Outcomes Study 36-Item Short-Form Health Survey, BDI=Beck Depression Inventory, VASF=Visual Analog Scale of Fatigue, FSI=Fatigue Scale Inventory, CGIS=Clinical Global Impression Scale, SIGH-D=Structured Interview Guide for the HAM-D

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 and is often associated with an inability to work. 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 modafinil 200mg daily, and two weeks of modafinil 400mg daily. The authors found that patients on the 200mg dose showed a significant improvement in fatigue compared with the placebo run in. Interestingly, this improvement compared to placebo was not demonstrated with the 400mg dose. This finding could be perceived two ways: 1) the 400mg dose is not as effective as the lower 200mg dose, or 2) 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.

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.

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 significantly 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.

Drug-Induced Sleepiness

A number of small-scale studies or case reports have been published evaluating the use of modafinil for drug-induced sleepiness. For some medications such as antipsychotics and narcotics, daytime sleepiness is an adverse effect that some wish to avoid. However, the concurrent use of a stimulant and a sedative-hypnotic makes little clinical sense. Currently, there are no well-supported studies that recommend the use of modafinil in drug-induced sleepiness.

Attention Deficit/Hyperactivity Disorder (ADHD)

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. 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]

Subsequent to a small open-label study[9], Rugino and Samsock[10] evaluated the use of modafinil 100-400mg daily in 22 children aged 5-15 years in a randomized, double-blind, placebo-controlled study. The authors found statistically significant improvements in the Test of Variables of Attention (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.

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 daily) 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.

Conclusion

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 strong supportive evidence.

Reviewed by Jim Slater, PharmD, Providence Health Plan

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