Modafinil: Is it ready for prime time?

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ABSTRACT

Psychostimulants have been used to treat many symptoms associated with advanced cancer. The primary role of psychostimulants in such cases is the treatment of symptoms such as cancer-related fatigue, opioid-induced sedation, depression, and cognitive dysfunction associated with malignancies. These uses for psychostimulants came after approval for treatment of disorders such as attention deficit disorder. Modafinil, a new psychostimulant, is following a similar path after its approval for use in attention deficit disorder in 1998. Modafinil has been used to treat fatigue associated with neurodegenerative disorders such as multiple sclerosis and amyotrophic lateral sclerosis. It is now being increasingly used for cancer-related symptoms targeted by psychostimulants. Preliminary evidence from literature review suggests that modafinil is efficacious in improving opioid-induced sedation, cancer-related fatigue, and depression. There is no evidence to support its use in the treatment of cognitive dysfunction related to cancer or to support its having analgesic properties. Well-designed, randomized, controlled clinical trials are still needed to further elucidate the precise role of this drug in the care of patients with cancer. Specifically, large placebo-controlled trials with modafinil must be conducted in patients with cancer, with specific attention paid to pain control, depression, cognitive function, and adverse effects.

Key words: modafinil, reticular activating system, psychostimulants

INTRODUCTION

Modafinil, 2-[(diphenylmethyl)sulphinyl]acetamide, is a schedule IV compound, approved by the Food and Drug Administration (FDA) in December 1998 for treatment of excessive daytime sleepiness in patients with narcolepsy.[1] Its stimulant properties led to its use in treating fatigue due to neurodegenerative disorders.[2,3] Clinical trial data suggest that modafinil has an excellent safety profile and is well tolerated.[4-6] As a stimulant, modafinil has been used increasingly for the palliation of symptoms for which psychostimulants are traditionally used, namely cancer-related fatigue, opioid-induced sedation, and depression. In recognition of modafinil's increasing use, this paper will review the current status of this substance in the treatment of cancer-related symptoms commonly targeted by psychostimulants and will examine whether its use is based on solid clinical evidence. The structure of modafinil is shown in Figure 1.

PHYSIOLOGY OF THE SLEEP–WAKE CYCLE

The neural pathway of the waking process, called the reticular activating system,[7] originates in the brainstem and sends projections from the brainstem and posterior hypothalamus throughout the forebrain.[8] Modern neuroanatomic tracer methods and immunohistochemical techniques have identified several nuclei as contributors to this arousal pathway. Important contributors include the cholinergic pedunculopontine, laterodorsal tegmental nuclei,[9] noradrenergic locus coeruleus, and serotoninergic dorsal and median raphe nuclei, as well as histaminergic projections from the tuberomammillary nucleus (lateral hypothalamus).[7] Cholinergic nuclei project to the thalamus, which then projects to the cortex. Aminergic nuclei project diffusely throughout the forebrain, regulating the activity of cortical and hypothalamic targets directly. Neurotransmitters such as acetylcholine, histamine, serotonin, and norepinephrine are activating. All activating neuronal groups become silent during sleep (both nonrapid eye movement, or NREM, and rapid eye movement, or REM), with the exception of the cholinergic pedunculopontine and laterodorsal tegmental nuclei, which fire intermittently during REM sleep. Table 1 summarizes the important nuclei and neurotransmitters involved in the sleep-wake cycle. Table 2 summarizes the activities of the nuclei important during the sleep-wake cycle.

Neurotransmitters such as γ-amino-butyric acid (GABA) and galanin, which originate in the ventrolateral preoptic nucleus (VLPO) of the hypothalamus, antagonize the proawakening influences of these neurotransmitters via inhibitory projections from the VLPO. The VLPO is also innervated in a reciprocal fashion by histaminergic axons from the tuberomammillary nucleus,

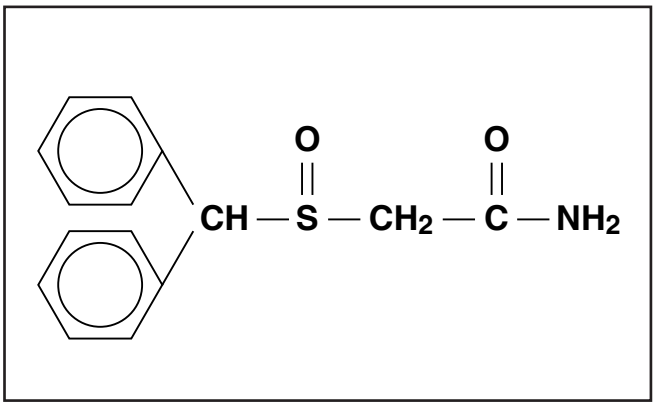

Figure 1. Molecular structure of modafinil.

noradrenergic terminals from the locus coeruleus, and serotoninergic inputs from the midbrain raphe nuclei.[10] In animal models, lesions placed in the VLPO can lead to reductions in both REM and NREM sleep.[11]

More recent discoveries have emphasized the role of the hypocretin/orexin peptides, which originate from the lateral hypothalamus and interact with all components of the arousal pathway. Orexin-containing neurons promote wakefulness. The hypocretin/orexin peptides also play a critical role in other physiological functions, such as activation of the sympathetic nervous system, appetite, and activation of the hypothalamic-pituitary-adrenal axis (directly or indirectly).[12] Their importance in the sleep-wake cycle is supported by their deficiency in the cerebrospinal fluid of patients with narcolepsy.[13]

Most sleep models hypothesize mutual inhibition between the VLPO and the major arousal systems. When VLPO neurons fire rapidly during sleep, they inhibit the monoaminergic cell groups, thus disinhibiting and reinforcing their own firing. Similarly, when monoamine neurons fire at a high rate during wakefulness, they inhibit the VLPO, thereby disinhibiting their own firing. This is analogous to what is described in engineering as a *flip-flop circuit*.[7] The two halves of a flip-flop circuit, by strongly inhibiting each other, create a feedback loop that is bistable, with two possible stable patterns of firing and a tendency to avoid intermediate states; in the case of the sleep-wake cycle, this prevents the inappropriate onset of sleep, which could be disastrous. This stability also offsets other potential influences that could shift transitions from wakefulness to sleep, such as circadian sleep drive. Orexin/hypocretin neurons are postulated to act as a "finger," pressing the flip-flop switch into the wakeful position and preventing inappropriate switching into the sleep position.[7]

MODAFINIL AND OTHER PSYCHOSTIMULANTS: MECHANISMS OF ACTION

Amphetamine, methylphenidate, and pemoline act neuropharmacologically by enhancing the amount of monoamines available within the synaptic cleft by either blocking uptake of dopamine or by facilitating catecholamine release from neurons.[14]

The predominant mode of action of modafinil is that of inhibition of GABA. This inhibition appears to allow release of dopamine, norepinephrine, and serotonin from their cells of origin as opposed to specific actions at the synapse. The alerting effect of modafinil is abolished by the α1-adrenoceptor antagonist prazosin, consistent with a possible role of the ascending noradrenergic system in the wakefulness-promoting effect of modafinil.[15]

Modafinil strongly increases Fos expression in tuberomammillary nuclei and orexin neurons, and activation of these neurons may be an essential component of modafinil's wake-promoting mechanism, resulting in dopaminergic activation of postsynaptic adrenergic receptors.[16] Modafinil may reinforce the action of the orexin nuclei.

PHARMACOLOGY

Pharmacokinetics

Modafinil is a racemic compound, whose l-isomer has a half-life approximately three times that of the d-isomer and accounts for the pharmacologic data available. Modafinil pharmacokinetics have not been studied in cancer patients. Modafinil is available in tablet form only. The half-life of modafinil after multiple doses is about 15 hours.[17] Modafinil exhibits linear kinetics upon multiple dosing of 200 to 600 mg/day in healthy volunteers, and steady state is reached after two to four days of dosing.[18]

Absorption and distribution

Absorption of modafinil tablets is rapid, with peak plasma concentrations occurring at 24 hours. Food may delay absorption. Modafinil is well distributed in body tissue, with an apparent volume of distribution (~ 0.9 L/kg) larger than the total volume of body water (0.6 L/kg). Modafinil is moderately bound to plasma protein (~ 60 percent, mainly to albumin).[19]

Metabolism and elimination

Modafinil is metabolized primarily in the liver (90 percent) through hydrolytic deamidation, S-oxidation, aromatic-ring hydroxylation, and glucuronide conjugation. Metabolites are renally excreted. The metabolites (modafinilic acid) of modafinil are inactive. Less than 10 percent of an administered dose is excreted as the parent compound. Chronic dosing may lead to decreased trough levels, suggesting autoinduction of metabolism. Modafinil pharmacokinetics are not affected by gender. Single-dose

Table 2. Activity of nuclei and neurotransmitters according to sleep stage			
Nuclei	**Awake**	**NREM**	**REM**
LDT/PPT	++	0	++
LC/DR/TMN	++	+	0
VLPO	0	+-++	++
Hypocretin/orexin	++	?	?

Adapted from Saper CB, Chou TC, Scammell TE: The sleep switch: Hypothalamic control of sleep and wakefulness. *Trends in Neurosciences.* 2001; 24(12): 726-731. DR, dorsal raphe nucleus; LC, locus coerulus; LDT, laterodorsal tegmental; NREM, non-rapid eye movement; PPT, pedunculopontine; REM, rapid eye movement; TMN, tuberomamillary nucleus; VLPO, ventrolateral preoptic nucleus.

or laboratory parameters were evident with modafinil treatment. Table 3 summarizes the incidence of adverse effects (> 5 percent) in studies comparing modafinil with placebo (n = 369). Modafinil has not been directly compared to other psychostimulants in clinical trials, so there has been no direct comparison of adverse effects. There are no adequate well-controlled studies in pregnant women. In laboratory mice, no evidence of teratogenicity has been shown.

MODAFINIL FOR THE TREATMENT OF OPIOID–INDUCED SEDATION

Although there have been no large, randomized, controlled trials for treatment of opioid sedation, use of psychostimulants such as methylphenidate can be useful in counteracting the sedative effects of opioids.[23,24] Webster and colleagues[25] retrospectively assessed the responses of patients who had been prescribed modafinil for opioid-induced sedation. These patients were routinely assessed for sedation using the Epworth Sleepiness Scale (ESS), a commonly used sedation scale. When modafinil was prescribed to treat opioid-induced sedation, there was a significant improvement in ESS scores between the first ESS measurement and the final ESS measurement while patients remained on modafinil treatment ($p = 0.023$). The average opioid dose (in morphine equivalents) at which modafinil was started was 536 mg/patient/day, and the average ending opioid dose was 810 mg/patient/day (mean change: + 274 mg/patient/day; $p = 0.027$). The average initial modafinil dose was 264 mg/patient/day, which increased to a final dose of 427 mg/patient/day (mean change: + 164 mg/patient/day; $p = 0.009$). It appears that modafinil can counteract opioid-induced sedation, allowing increments in opioid doses. There were no additive toxicities when modafinil was combined with opioids.

CANCER–RELATED FATIGUE

There is empiric evidence that stimulants such as methylphenidate may have a beneficial effect on cancer-related fatigue in some patients.[26,27] Modafinil has been studied in cancer patients suffering from fatigue that persisted after therapy.[28] Fifty-one women (mean age: 54.5 years) who had completed breast cancer treatment an average of 23.5 months earlier and who were reporting persistent fatigue were enrolled in a one-month open-label trial of modafinil (200 mg with breakfast). The mean fatigue-severity level at baseline for the 51 enrollees was 6.9 on a scale where 0 represented "not present" and 10 was equal to "as bad as you can imagine." After treatment, mean fatigue severity had fallen to a mean of 3.7 ($p < 0.01$). The majority (86 percent) reported at least a 1-point improvement over the course of the one-month study. Patient-reported global effectiveness measured after treatment supported the finding that modafinil was an effective treatment for fatigue; the mean rating was 5.0 (SD = 2.0; with 1 meaning "no benefit" and 7 meaning "great improvement"). Adverse effects such as agitation occurred in three patients and led to their dropping out of the trial. Fifty-one percent of the patients reported improvement in sleep, and 51 percent reported less drowsiness. Additional improvements reported by a majority of patients were an increase in general activity (64 percent), improved mood (63 percent), improved walking ability (63 percent), normal work ability (66 percent), better relations with other people (66 percent), and greater enjoyment of life (61 percent).

MODAFINIL AND PAIN CONTROL

In animal studies, psychostimulant drugs have been shown to possess intrinsic analgesic properties and to have the ability to enhance the analgesic properties of opioids when both types of drugs are given in combination. Studies with human subjects strongly suggest that psychostimulant drugs enhance opioid analgesia, possibly by enhancing alertness, permitting larger doses of opioids, or possessing analgesic properties in their own right.[23,24,27,29]

Table 1. Important nuclei and neurotransmitters important in the sleep/wake cycle				
Reticular activating system nuclei	**Neurotransmitter**	**Function**	**Link**	**Overall function**
PPT, LDT	acetylcholine	activation	hypothalamus/thalamus/BF	maintain wakeful state and REM sleep
DRN	serotonin	activation	hypothalamus/thalamus/BF	maintains wakeful state slows with NREM sleep
LC	noradrenergic	activation	hypothalamus/thalamus/BF	maintains wakeful state slows with NREM sleep
Hypothalamic nuclei				
VLPO	GABA galanin	inhibitory	tuberomamillary nucleus, LC, DRN, LDT, PPT	inhibit and inhibited by RAS nuclei
TMN	histamine	activates hypothalamus	ventrolateral preoptic area	maintains wakeful state slows with NREM sleep
lateral hypothalamus	hypocretic/orexin	activates hypothalamus	LDT, PPT, DRN, TMN, LC, BF	stabilize firing of neurons that maintain REM and wakeful state
thalamus	acetylcholine	maintenance of awake state and NREM sleep	cortex	receives input from RAS to maintain awake state NREM sleep
BF	acetylcholine	activation	cortex	helps maintain awake state with thalamus

BF, basal forebrain; DRN, dorsal raphe nucleus; GABA, γ-aminobutyric acid; LC, locus coerulus; LDT, laterodorsal tegmental; NREM, nonrapid eye movement; PPT, pedunculopontine; RAS, reticular activating system; REM, rapid eye movement; TMN, tuberomamillary nucleus; VLPO, ventrolateral preoptic nucleus.

studies suggest that age can affect the clearance of modafinil (up to 20 percent), with plasma levels in patients (age range: 67 to 87 years) reaching nearly twice those of properly matched younger patients. Severe renal insufficiency (creatinine clearance = 20 mL/min) does not affect the pharmacokinetics of modafinil. Patients with liver failure (Childs B, C) can experience a reduction in clearance of up to 60 percent and should have their dosage reduced (see schedule of administration).[19]

Drug interactions

Modafinil interacts with the cytochrome P-450 system. It reversibly inhibits CYP2C9 and induces CYP3A4, leading to the potential for drug interactions. At this time, the actual pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Inhibition of CYP2C9 can potentially lead to increased retention levels of drugs such as phenytoin, diazepam, propranolol, and warfarin.[19] Thus far, single-dose studies involving healthy volunteers have not resulted in any changes in the known pharmacokinetics of warfarin.[20] Induction of CYP3A4 can lead to decreased levels of triazolam and ethinyl estradiol (at doses of 400 mg).[21] One case report describes a lowering of cyclosporine levels by 50 percent one month after the patient had been started on modafinil (200 mg/day).[22] Coadministration of dextroamphetamine and methylphenidate did not alter the pharmacokinetics of modafinil.[17] Overall, no significant clinical consequences of these interactions have been reported. However, until further information is available, caution should be used when modafinil is administered with other drugs that interact with CYP2C9 and CYP3A4.

Adverse effects

The results of two double-blind phase III trials of modafinil in more than 550 patients with narcolepsy showed a slightly higher incidence of adverse events in the modafinil group than in the placebo group.[19] Headache, nausea, and rhinitis were the only adverse effects experienced by patients in two other double-blind, placebo-controlled studies.[5,6] No clinically significant effects on vital signs, electrocardiographic findings,

Table 3. Adverse effects of modafinil (incidence ≥ 5 percent)			
Organ system	**Adverse effect**	**Placebo (n = 185) (percent)**	**Modafinil (n = 389) (percent)**
Central nervous system	Headache	40	50
	Nervousness	6	8
	Dizziness	4	5
	Insomnia	1	5
Digestive	Nausea	4	13
	Diarrhea	4	8
	Dry mouth	1	5
	Anorexia	1	5
	Dyspepsia	4	5
Respiratory	Rhinitis	6	7
Other	Back pain	6	7
Adapted from package insert.			

Twelve healthy subjects with acute pain (e.g., finger pressure and ischemic pain) were assessed in a randomized, double-blind crossover study of placebo and modafinil (400 mg once daily). The single-dose study failed to demonstrate any analgesic properties of modafinil. Currently, there is no evidence that modafinil has intrinsic analgesic properties. It may enable larger doses of opioids to be given by counteracting sedation.

MODAFINIL FOR THE TREATMENT OF DEPRESSION

The reported prevalence of depression among cancer patients varies from 0 to 38 percent for major depression to 0 to 58 percent for depression spectrum syndromes, depending on the criteria for diagnosis and methodology used to define depression, as well as the populations studied. Depression is highly associated with oropharyngeal (22 to 57 percent), pancreatic (33 to 50 percent), breast (1.5 to 46 percent), and lung (11 to 44 percent) cancers.[30] Depression increases with disease stage and affects compliance and ability to care for one's self. It is also associated with poor symptom control, pain, and fatigue.[31] Psychostimulants have a role in the management of depressed medically ill persons and in cancer patients.[26] In addition, because of their rapid onset of action compared with antidepressants, psychostimulants such as methylphenidate are frequently used to "bridge" patients until antidepressants become effective, especially in patients with a short life expectancy and in patients with depression and fatigue.

Most studies evaluating modafinil in depression have been limited to "augmentation studies" where modafinil was used to alleviate sedation, depression, and fatigue in patients already receiving antidepressants, usually selective serotonin-reuptake inhibitors (SSRIs). These studies did not include cancer patients. One multicenter, placebo-controlled study of modafinil augmentation evaluated 311 patients who had a partial response to SSRI monotherapy (= eight weeks) or had been at a stable dosage for four weeks or longer but still had significant depression, sedation, and fatigue as measured by the 31-item Hamilton Rating Scale for Depression (HAM-D) (scores of 14 to 26), the ESS (scores = 10), and the Fatigue Severity Scale (FSS) (scores = 4). Patients were randomized to augmentation therapy with either modafinil 200 mg/day or with placebo for eight weeks. Assessments of response to modafinil/placebo included scores on the ESS, Clinical Global Impressions of Improvement scale (CGI-I) (assesses magnitude of effect between antidepressants and placebo), 31-item and 17-item HAM-D, FSS, Brief Fatigue Inventory, and Montgomery-Asberg Depression Rating Scale. Modafinil significantly improved patients' overall clinical condition compared with placebo on the basis of CGI-I scores ($p = 0.02$), and there were trends toward greater mean reductions in sedation, depression, and fatigue when compared with placebo.[32]

An earlier study evaluated 136 patients with major depression with partial response to antidepressant therapy given for at least six weeks.[33] Most patients (82 percent) were fatigued, and more than half of the patients (51 percent) felt sedated. Seventy-five percent had been taking SSRIs, and 20 percent had been taking non-SSRIs such as venlafaxine, trazodone, nefazodone, mirtazapine, and bupropion. Again, there were no cancer patients included. Patients received once-daily doses (100 to 400 mg) of modafinil or matching placebo as adjunct treatment to ongoing antidepressant therapy. The

effects of modafinil were evaluated using the HAM-D, the FSS, the ESS, the Clinical Global Impressions of Change (CGI-C), and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36). Modafinil rapidly improved fatigue and daytime wakefulness, with significantly greater mean improvements from baseline when compared with placebo with regard to fatigue (FSS) scores at week two ($p < 0.05$) and sleepiness (ESS) scores at week one ($p < 0.01$); the differences between modafinil and placebo at week six were not statistically significant. It seems that modafinil can have a rapid onset of action, similar to other psychostimulants such as methylphenidate. The effects may wane with continued usage. In summary, modafinil is safe to use in patients with depression. It appears to be useful in treating fatigue and sleepiness associated with depression and antidepressant use and, like other psychostimulants, can rapidly improve fatigue and somnolence.

EFFECTS ON COGNITIVE FUNCTION

Psychostimulants enhance cognitive function. Agents such as methylphenidate have been shown to be beneficial in hypoactive delirium[34,35]; improving cognition problems associated with opioid use[35]; and improving some attentional and social deficits among survivors of childhood ALL, childhood brain tumors,[36] and adult gliomas.[37] So far, understanding of the cognition-enhancing effects of modafinil and its relevant neurobiological mechanisms is incomplete. When tested in normal human hosts who are not sleep deprived, improvements are limited to the span of immediate verbal recall and short-term visual recognition memory, which is insufficient to be considered cognition enhancing.[38] There does not appear to be a dose relationship associated with these cognitive improvements.

ABUSE POTENTIAL

Jasinski and coworkers[39] evaluated the abuse liability of modafinil. Their work showed that modafinil at doses less than 800 mg did not produce the euphoric effects seen with other psychostimulants. The study did demonstrate euphoric psychoactivity typical of amphetamines and other prototypic drugs of abuse at doses of 800 mg/day. Overall, abuse of psychostimulants in medically ill patients has not been reported.

COST COMPARISON WITH METHYLPHENIDATE

Average wholesale prices (AWP) (Red Book 2004) are in US dollars as follows:

Methylphenidate		Modafinil	
5 mg	AWP: 0.33	100 mg	AWP: 6.19
10 mg	AWP: 0.48	200 mg	AWP: 8.55
20 mg	AWP: 0.69		

SCHEDULE OF ADMINISTRATION

The recommended dosage of modafinil is 200 mg given once a day. Dosages up to 400 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that this dosage confers additional benefit beyond that of the 200-mg dosage. Switching from methylphenidate to modafinil was well tolerated with or without a between-treatment washout period or when the methylphenidate dosage was gradually tapered during initiation of modafinil therapy.[13]

CONCLUSION

Modafinil appears to be a well-tolerated medication that has many characteristics of psychostimulants but with a different mechanism of action. Currently, there is no evidence that it has analgesic properties or can benefit cognitive functioning. Studies claiming improvement in opioid-induced sedation and cancer-related fatigue have been retrospective (sedation) or prospective open-label (fatigue). There is evidence that modafinil can be used as a psychostimulant in the treatment of depression to counteract adverse effects of antidepressants and provide improvements in mood and energy before the antidepressants work; however, further testing in cancer patients is warranted. As with other psychostimulants, there is still the need for well-designed, randomized, controlled clinical trials to further elucidate the precise role of this drug in the care of terminally ill patients. Specifically, large, placebo-controlled trials with modafinil must be conducted in patients with cancer, with attention to specific outcomes including pain control, depression, cognitive function, adverse effects, and duration of action. Like methylphenidate, further trials may confirm the preliminary evidence that modafinil can treat opioid-induced sedation, fatigue, depression, or pain. If further trials can establish a comparative efficacy to other psychostimulants and/or fewer adverse effects, modafinil may become an option when other psychostimulants cause adverse effects or when their effects wane. Unfortunately, its cost may be prohibitive for some hospices.

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