Neuropsychopharmacology 2008) 33, 1477–1502

www.neuropsychopharmacology.org

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Modafinil A Review of Neurochemical Actions and Effects on Cognition

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Modafinil (2-[(Diphenylmethyl) sulfinyl] acetamide, Provigil) is an FDA-approved medication with wake-promoting properties. Pre-clinical studies of modafinil suggest a complex profile of neurochemical and behavioral effects, distinct from those of amphetamine. In addition, modafinil shows initial promise for a variety of off-label indications in psychiatry, including treatment-resistant depression, attention-deficit/hyperactivity disorder, and schizophrenia. Cognitive dysfunction may be a particularly important emerging treatment target for modafinil, across these and other neuropsychiatric disorders. We aimed to comprehensively review the empirical literature on neurochemical actions of modafinil, and effects on cognition in animal models, healthy adult humans, and clinical populations. We searched PubMed with the search term 'modafinil' and reviewed all English-language articles for neurochemical, neurophysiological, cognitive, or information-processing experimental measures. We additionally summarized the pharmacokinetic profile of modafinil and clinical efficacy in psychiatric patients. Modafinil exhibits robust effects on catecholamines, serotonin, glutamate, gamma amino-butyric acid, orexin, and histamine systems in the brain. Many of these effects may be secondary to catecholamine effects, with some selectivity for cortical over subcortical sites of action. In addition, modafinil (at well-tolerated doses) improves function in several cognitive domains, including working memory and episodic memory, and other processes dependent on prefrontal cortex and cognitive control. These effects are observed in rodents, healthy adults, and across several psychiatric disorders. Furthermore, modafinil appears to be well-tolerated, with a low rate of adverse events and a low liability to abuse. Modafinil has a number of neurochemical actions in the brain, which may be related to primary effects on catecholaminergic systems. These effects are in general advantageous for cognitive processes. Overall, modafinil is an excellent candidate agent for remediation of cognitive dysfunction in neuropsychiatric disorders.
Neuropsychopharmacology (2008) **33,** 1477–1502; doi:10.1038/sj.npp.1301534; published online 22 August 2007

Keywords: modafinil; dopamine; norepinephrine; cognition; psychiatry

INTRODUCTION

Modafinil (2-[(Diphenylmethyl) sulfinyl] acetamide; brand name Provigil in the United States) is a novel wake-promoting agent first marketed in France in the early 1990s, as a treatment for the excessive somnolence as a feature of narcolepsy. It is currently approved by the United States Food and Drug Administration as a schedule IV agent to treat excessive daytime sleepiness in narcolepsy, shift work sleep disorder, and obstructive sleep apnea/hypopnea syndrome. It has been popularly categorized as a psychostimulant due to its wake-promoting properties. However, it has shown a number of effects on physiology and behavior in both animal models and in humans, which suggest a divergent mechanism of action compared to amphetamine (described in detail below). This includes a lower liability to abuse, and a lower risk of adverse effects on organ systems such as the cardiovascular system. As a result, great interest has emerged in the possibility that modafinil may demonstrate clinical efficacy in a number of medical and psychiatric conditions currently treated with stimulants, such as various fatigue syndromes, treatment-resistant depression, and attention-deficit/hyperactivity disorder (ADHD). This interest has spawned numerous clinical trials of modafinil undertaken and reported across a range of these illnesses in recent years. These studies are summarized below, and more comprehensively reviewed elsewhere (Ballon and Feifel, 2006). The range of off-label uses for modafinil nevertheless appears to be outpacing the growth of this empirical literature, despite a lack of clear consensus about the precise neurochemical mechanism of action of this agent, inadequate clinical experience and a dearth of empirical data addressing the long-term use of this agent.

Among the various potential treatment targets for modafinil found across neurology and psychiatry, cognitive dysfunction is perhaps the target with the most critical need for truly novel pharmacotherapies, given the importance of cognition to clinical outcome in these disorders and the relative paucity of treatment options for cognition existing

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Received 1 May 2007; revised 14 July 2007; accepted 16 July 2007

in the current pharmacopoeia. The emerging emphasis on cognitive dysfunction in neuropsychiatric disorders, together with the well-established effects of modafinil on arousal and activity, has inspired an emerging literature addressing the pro-cognitive effects of modafinil. These studies suggest that this agent is a promising candidate agent for cognitive dysfunction, particularly in disorders such as ADHD and schizophrenia where cognitive deficits are core, disabling features. Therefore, both the expanding list of off-label uses for modafinil and the prospects for identifying a novel pro-cognitive agent necessitate a summary and integration of the empirical literature existing to date. In this review, we briefly summarize the pharmacokinetic profile of modafinil in humans. We then outline and attempt to synthesize the complex literature addressing the neurochemical effects of modafinil, particularly as a potential treatment for cognitive dysfunction. We review the empirical literature where effects of modafinil on cognition have been tested, in animal models, healthy humans, and clinical populations. Finally, we summarize the empirical studies of clinical effects of modafinil in psychiatric disorders. Overall, this literature appears to provide a clear rationale for further investigation of the neural basis of modafinil effects on cognition, both to elaborate the role of central neurotransmitter systems in the modulation of normal cognition, and to evaluate modafinil as a candidate agent for the treatment of cognitive dysfunction.

PHARMACOKINETICS OF MODAFINIL IN HUMANS

Modafinil is a racemate, with the two enantiomers being approximately equipotent in behavioral effects in mice, but different in pharmacokinetic profile (reviewed by Robertson and Hellriegel, 2003). The R-enantiomer (armodafinil) appears to reach higher plasma concentrations than the racemic form between 6–14 h after administration, with an associated longer duration of wake-promoting activity in healthy adults (Dinges *et al*, 2006). Modafinil can be reliably determined in plasma and urine (Schwertner and Kong, 2005; Tseng *et al*, 2005), and is readily absorbed (40–65 , as measured by urinary recovery) after single (Wong *et al*, 1999a) or multiple oral doses (Wong *et al*, 1999b), reaching peak plasma concentrations 2–4 h after administration (Wong *et al*, 1999a). The presence of food in the gastrointestinal tract can slow the rate but does not affect the total extent of absorption. Steady-state plasma concentrations are achieved between 2 and 4 days with repeated dosing. It is highly lipophilic, and approximately 60 bound to plasma proteins, primarily albumin. Major pharmacokinetic parameters are independent of doses in the range of 200–600 mg/day (Robertson and Hellriegel, 2003). The major circulating metabolites modafinil acid and modafinil sulfone do not appear to exert any significant activity in the brain or periphery (Robertson and Hellriegel, 2003). The elimination half-life is approximately 12–15 h (Wong *et al*, 1999a), and single daily dosing is adequate and common in clinical practice. Elimination occurs primarily in the liver, via amide hydrolysis and a lesser component by cytochrome P450-mediated oxidation. Excretion occurs in the urine, with less than 10 of the oral dose excreted as the unchanged drug. Elimination is slowed in the elderly or in individuals with hepatic or renal impairment (Wong *et al*, 1999a, b). Some drug–drug interactions are apparent with modafinil. *In vitro*, modafinil exerts a reversible inhibition of CYP2C19 (in human liver microsomes), and a smaller but concentration-dependent induction of CYP 1A2, 2B6, and 3A4, and suppression of 2C9 activity, in primary cultures of human hepatocytes (Robertson *et al*, 2000; Wong *et al*, 1999b). The 2C9 suppression observed *in vitro* is much less apparent *in vivo*. The modafinil metabolite modafinil sulfone also inhibits 2C19 with a comparable K_i. The inhibition of 2C19 may be significant for those minority of patients who are 2D6-deficient and taking concurrent medications that are substrates for 2D6 with ancillary metabolic degradation via 2C19 (eg, fluoxetine, clomipramine). Clinical studies have found significant interactions of modafinil with ethinylestradiol and triazolam (through CYP3A4 induction in the gastrointestinal system) (Robertson *et al*, 2002b), although not with methylphenidate (Hellriegel *et al*, 2001; Wong *et al*, 1998a), dextroamphetamine (Hellriegel *et al*, 2002; Wong *et al*, 1998b) or warfarin (Robertson *et al*, 2002a).

NEUROCHEMICAL EFFECTS OF MODAFINIL

Modafinil Effects on Catecholamine Systems

The empirical literature addressing modafinil effects on central neurotransmitter systems is summarized in Table 1. Modafinil is structurally unrelated to amphetamine and has a differing profile of pharmacological and behavioral effects (Table 2). An early study found modafinil to exhibit only a modest affinity for the DA transporter (DAT) ($IC_{50} = 3.19\,\mu M$) in a rodent brain preparation, and no apparent specific binding to a range of other monoamine or neuropeptide receptors or transporters, nerve membrane ion channels, nor direct effects on second messenger systems in the brain (Mignot *et al*, 1994). However, a recent positron emission tomography (PET) study of rhesus monkeys found significant binding of the DAT (using [^{11}C]CFT) in the striatum (54 occupancy at 8 mg/kg) and norepinephrine (NE) transporter (NET) (using [^{11}C]MeNER) in the thalamus (44 occupancy at 8 mg/kg) (Madras *et al*, 2006). In addition, using *in vitro* human monoamine transporter preparations, binding to DAT and NET was confirmed with IC_{50} 10 μM (and IC_{50} 500 μM for the 5HT transporter). In this study, the *in vitro* potency of modafinil in binding DAT and NET was low relative to methylphenidate, buproprion, or benztropine; however, modafinil showed DAT occupancy by PET that was comparable to methylphenidate at clinically relevant doses. In addition, the doses used to detect DAT binding were 2–8 times lower than that which promotes wakefulness in monkeys (Hermant *et al*, 1991). Furthermore, whereas modafinil 10 μg did not exhibit direct binding to the trace amine receptor 1 (TA1) *in vitro*, it did augment the stimulation of TA1 by phenylethylamine in cells expressing DAT and NET. There is recent evidence for modulatory interactions between the TA1 receptor and both DA neuron activity in rats (Geracitano *et al*, 2004) and DAT activity in primates (Miller *et al*, 2005; Xie and Miller, 2007; Xie *et al*,

Table 1 Effects of Modafinil Mediated by Central Neurotransmitter Systems

Transmitter system	Effect of modafinil treatment	Modafinil dose/route	Measurement method	Species/preparation	Reference
Dopamine					
	Inhibition of DA cell firing in VTA/SN; blocked by Sulpiride 10 μM but not by Prazosin	20 μM	Extracellular recording	Rat brain slice	Korotkova *et al*, 2006
	Hyperpolarization of VTA neurons, blocked by Sulpiride 10 μM	20–50 μM	Whole-cell patch clamp	Isolated VTA neurons	
	No effect on mesencephalic DA neuron activity	128 mg/kg i.p.	Single-unit recording	Rat (anesthetized)	Akaoka *et al*, 1991
	Striatal DAT occupancy: 6, 35, 54%	2, 5, 8 mg/kg i.v.	PET with [^{11}C]CFT	Rhesus monkey	Madras *et al*, 2006
	DAT binding	$IC_{50} = 6.4$ μM	[^{3}H] DA	Human embryo kidney	
	DAT binding	$IC_{50} = 3.19$ μM	[^{3}H] WIN 35428	Guinea pig striatum	Mignot *et al*, 1994
	Extracellular DA: ↑ in PFC, medial hypothalamus	128 mg/kg i.p.	Intracranial microdialysis	Rat	de Saint Hilaire *et al*, 2001
	Extracellular DA: ↑ in striatum of orexin-2-KO narcoleptic dogs; effect on waking abolished in DAT-KO mice	5 mg/kg i.v. (dog); 90 mg/kg i.p. (mouse)	Intracranial microdialysis (dog); EEG (mouse)	orexin-2-KO narcoleptic dog; DAT-KO mouse	Wisor *et al*, 2001
	Extracellular DA: minimal ↑ in nucleus accumbens, only at 300 mg/kg	100, 300 mg/kg i.p.	Intracranial microdialysis	Rat	Ferraro *et al*, 1997b
	Extracellular DA: ↑ in nucleus accumbens, blocked partly by anandamide	10 μg/5 μl i.c.v.	Intracranial microdialysis	Rat	Murillo-Rodriguez *et al*, 2007
	cortical GABA by modafinil abolished in 6-OHDA-lesioned animals	30 mg/kg s.c. for 7 d	Intracranial microdialysis	Guinea pig	Tanganelli *et al*, 1994
	Prevents loss of DA or non-DA neurons in SN after MPTP	100 mg/kg i.p.	Tyr-Hydroxylase-IR	C57bl/6 mouse	Aguirre *et al*, 1999
	Prevents loss of DA neurons in SN, DAT in striatum, or DA in SN/striatum, after MPTP	10–100 mg/kg i.p. for 2 weeks	TH-IR; intracranial microdialysis	black mouse	Fuxe *et al*, 1992
Norepinephrine					
	Thalamic NET occupancy: 16, 44%	5, 8 mg/kg i.v.	PET with [^{11}C]MeNER	Rhesus monkey	Madras *et al*, 2006
	NET binding	$IC_{50} = 35.6$ μM	[^{3}H] NE	Human Embryo Kidney	
	No effect on pontine NE neuron activity	128 mg/kg i.p.	Single-unit recording	Rat (anesthetized)	Akaoka *et al*, 1991
	Extracellular NE: ↑ in PFC, medial hypothalamus	128 mg/kg i.p.	Intracranial microdialysis	Rat	de Saint Hilaire *et al*, 2001
	Augmentation of NE inhibition of VLPO neuron activity; effect blocked by nisoxetine; no effect of modafinil alone	200 μM pre-treatment	Extracellular recording	Rat brain slice	Gallopin *et al*, 2004
	Extracellular GABA: no modafinil effect in cortex in prazosin pre-treated rats	30 mg/kg i.p.	Intracranial microdialysis	Rat	Tanganelli *et al*, 1995
	Effect on activity abolished in $_{1B}$-knockout mouse or by i.c.v. terazosin, not by i.c.v. BMY7378 ($_{1D}$)	20, 40 mg/kg i.p.	Observed movement	$_{1B}$-knockout mouse	Stone *et al*, 2002a
	Effect on waking preserved after DSP-4 treatment (NE toxin) and reversed after DSP-4 by terazosin, blunted by quinpirole	90 mg/kg i.p.	EEG	Mouse	Wisor and Eriksson, 2005

Table 1 Continued

Transmitter system	Effect of modafinil treatment	Modafinil dose/route	Measurement method	Species/preparation	Reference
	Effect on waking: attenuated by phentolamine, prazosin, propranolol, but not by haloperidol; effect on temperature reversed by prazosin	1, 2.5, 5 mg/kg p.o.	EEG; thermistor	Cat	Lin *et al*, 1992
	Effect on motor activity: reversed by prazosin, reserpine but not sulpiride or MPT	32–128 mg/kg i.p.	Actimetry	Mouse	Rambert *et al*, 1993
	Effect on nocturnal activity reversed by prazosin	16, 32, or 64 mg/kg p.o.	Observed movement	Rhesus Monkey	Hermant *et al*, 1991
	Effect on motor activity: reversed by prazosin, phenoxybenzamine and reserpine but not by haloperidol, sulpiride, phentolamine, yohimbine, propranolol or MPT	32–128 mg/kg i.p.	Actimetry	Mouse	Duteil *et al*, 1990
Serotonin					
	5HT binding	IC_{50} 500 μM	[^{3}H] 5HT	Human Embryo Kidney	Madras *et al*, 2006
	Extracellular 5HT: ↑ in PFC, medial hypothalamus	128 mg/kg i.p.	Intracranial microdialysis	Rat	de Saint Hilaire *et al*, 2001
	Extracellular 5HT: ↑ frontal cortex, central amygdala, dorsal raphe, all dose-dependent; ↑ mPOA and post hypothal only @ 100 mg/kg	10–100 mg/kg i.p.	Intracranial microdialysis	Rat	Ferraro *et al*, 2000, 2002
	Extracellular 5HT: ↑ effect of fluoxetine in frontal cortex and dorsal raphe, and of low-dose imipramine in frontal cortex; no effect of modafinil alone	3 mg/kg i.p.	Intracranial microdialysis	Rat	Ferraro *et al*, 2005
	Extracellular GABA: modafinil effect in mPOA, post hypothalamus after MDL72222 1 μM methysergide	100 mg/kg i.p.	Intracranial microdialysis	Rat	Ferraro *et al*, 1996
	Extracellular GABA: modafinil effect in cortex in i.c.v. 5,7-DHT-treated rats	30 mg/kg i.p.	Intracranial microdialysis	Rat	Tanganelli *et al*, 1995
	Extracellular GABA: modafinil effect in cortex after ketanserin or methysergide	3–30 mg/kg s.c.	Epidural cup	Rat	Tanganelli *et al*, 1992
	[^{3}H] 5HT efflux: no effect of modafinil	0.3–30 μM	Spontaneous, K^+-evoked tritium efflux	Rat frontal cortex synaptosome	Ferraro *et al*, 2001
	↑ K^+-evoked tritium efflux, enhanced by paroxetine; no effect on spontaneous efflux	1–10 μM	Spontaneous, K^+-evoked tritium efflux	Rat cortical slice	Ferraro *et al*, 2000, 2001
Glutamate					
	Extracellular Glutamate: ↑ in vmThal, vlThal, Hpc; all effects dose-related	30–300 mg/kg i.p.	Intracranial microdialysis	Rat	Ferraro *et al*, 1997a
	Extracellular Glutamate: ↑ in striatum only @ 300 mg/kg; no change in pallidal or SN glutamate	30–300 mg/kg i.p.	Intracranial microdialysis	Rat	Ferraro *et al*, 1998