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Perspective

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.
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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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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]Me-NER) 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 $IC_{50} < 10\,\mu M$ (and $IC_{50} > 500\,\mu M$ 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 α_{1B}-knockout mouse or by i.c.v. terazosin, not by i.c.v. BMY7378 (α_{1D})	20, 40 mg/kg i.p.	Observed movement	α_{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 αMPT	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 αMPT	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

Table 1 Continued

Transmitter system	Effect of modafinil treatment	Modafinil dose/route	Measurement method	Species/preparation	Reference
	Extracellular Glutamate: ↑ in mPOA, post hypothalamus; effects blocked by 1 μM local bicuculline	30–300 mg/kg i.p.	Intracranial microdialysis	Rat	Ferraro *et al*, 1999
	No effects on glutamate uptake in hypothalamus	1–33 μM	[^{3}H] glutamate uptake	Rat brain slice or synaptosomes	
	Inhibition of glutamate neurotoxicity	0.3–1 μM	Electrically-evoked [^{3}H] GABA release	Rat primary cortical culture	Antonelli *et al*, 1998
	↑ Glutamine synthetase in cortex	128 mg/kg i.p.	mRNA content	Northern blot hybridization	Touret *et al*, 1994
	No effects on synthesis of hypothalamic Glutamate	100 mg/kg i.p.	[^{3}H] Glutamate synthesis	Rat brain synaptosomes	Perez de la Mora *et al*, 1999
	↑ Glutamate-Glutamine pool, Aspartate pool	600 mg/kg i.p.	2D COSY ^{1}H-NMR	Rat	Pierard *et al*, 1995
GABA					
	Extracellular GABA: ↓ in cortex	30 mg/kg s.c. one-dose or 7d	Intracranial microdialysis	Guinea pig	Tanganelli *et al*, 1992, 1994, 1995
	Extracellular GABA: ↓ in mPOA, post hypothalamus; effects neg correlated with modafinil effects on glutamate	30–300 mg/kg i.p.	Intracranial microdialysis	Rat	Ferraro *et al*, 1996, 1999
	Extracellular GABA: ↓in striatum, pallidum, SN; no effects @ 30 mg/kg	30–300 mg/kg i.p.	Intracranial microdialysis	Rat	Ferraro *et al*, 1998
	Extracellular GABA: ↓ in vmThal, vlThal, Hpc; all effects only @ 300 mg/kg	30–300 mg/kg i.p.	Intracranial microdialysis	Rat	Ferraro *et al*, 1997a
	Extracellular GABA: ↓ in accumbens	100, 300 mg/kg i.p.	Intracranial microdialysis	Rat	Ferraro *et al*, 1997b
	No inhibition of GABA neurons in VTA/SN	20 μM	Extracellular recording	Rat brain slices	Korotkova *et al*, 2006
	No effects on synthesis of hypothalamic GABA	100 mg/kg i.p.	[^{3}H] GABA synthesis	Rat brain synaptosomes	Perez de la Mora *et al*, 1999
Orexin					
	↑ Fos in orexin neurons in perfornical area	150 mg/kg i.p.	Immunohisto-chemistry	Mice	Chemelli *et al*, 1999
		75 mg/kg i.p.	Immunohisto-chemistry	Rat	Scammell *et al*, 2000
	No binding to orexin-1 receptor	IC_{50} > 10 μM	^{125}I-human-orexin B displacement	Transfected Chinese Hamster Ovary cells	Wieland *et al*, 2002
	No change in Fos-IR, and ↑ effect of modafinil on waking EEG, in orexin-null mice	10, 100 mg/kg i.p.	Immunohisto-chemistry; EEG, time awake/asleep	Orexin-null mice	Willie *et al*, 2005
	No change in effects on extracellular DA in striatum, or wake-promoting activity, in orexin-2 receptor-null narcoleptic dogs	5 mg/kg i.v.	Intracranial microdialysis; time awake	Orexin-2 receptor-null narcoleptic dogs	Wisor *et al*, 2001
Histamine					
	Extracellular HA: ↑ in ant hypothalamus but not with intra-TMN injection	150 mg/kg i.p. or 1 nmol i.c.v.	Intracranial microdialysis	Rat	Ishizuka *et al*, 2003

Table 2 Studies which have Directly Compared Modafinil and Classic Catecholaminergic Psychostimulant Agents

Experimental measure	Species/preparation	Modafinil dose/ route	Psychostimulant for comparison	Stimulant dose/route	Modafinil effects	Stimulant effects	Reference
% DAT occupancy using [^{11}C] CFT and PET	Rhesus monkey	8 mg/kg i.v.	Methylphenidate	0.3 mg/kg i.v.	54% occupancy	51% occupancy	Madras *et al*, 2006
Inhibition of [^{3}H] DA transport	Human embryonic kidney		Methylphenidate		$IC_{50} = 6390$ nM	$IC_{50} = 25.4$ nM	
Inhibition of [^{3}H] NE transport	Human embryonic kidney		Methylphenidate		$IC_{50} = 35{,}600$ nM	$IC_{50} = 26.5$ nM	
Inhibition of [^{3}H] WIN 35428 binding	Guinea pig striatum		Cocaine		$IC_{50} = 3190$ nM	$IC_{50} = 46.2$ nM	Mignot *et al*, 1994
Inhibition of DA neuron activity in mesencephalon	Rat single-unit	128 mg/kg i.p.	Amphetamine	5 mg/kg i.p.	Firing rates 99–104%	Firing rates 0%	Akaoka *et al*, 1991
Inhibition of NE neuron activity in pons			Amphetamine	1 mg/kg i.p.	Firing rates 85–105%	Firing rates 13%	
Extracellular accumbens DA by microdialysis	Rat	100, 300 mg/kg i.p.	Amphetamine	1 mg/kg i.p.	Peak ↑ 61%	Peak ↑ 925%	Ferraro *et al*, 1997b
Extracellular accumbens GABA by microdialysis			Amphetamine	1 mg/kg i.p.	Nadir ↓24%	0% change	
Catechol oxidation by *in vivo* votammetry	Mouse	16–256 mg/kg i.p.	Amphetamine	2, 4, 8 mg/kg i.p.	Minimal decrease in catechol levels; no effect after pargyline	Biphasic response: larger ↓ catechol (*vs* modafinil) at 2 or 4 mg/kg; no change at 8 mg/kg; ↑ after pargyline	De Sereville *et al*, 1994
			Methylphenidate	16, 32, 64 mg/ kg i.p.		At 32 or 64 mg/kg: ↑ catechol; dose-dependent ↑ after pargyline	
c-Fos immunoreactivity	Cat	5 mg/kg i.p.	Amphetamine	1 mg/kg i.p.	Greater labeling in anterior hypothalamus, SCN, PAG	Greater labeling in caudate, accumbens, mediofrontal and temporal cortex, amygdala	Lin *et al*, 1996
			Methylphenidate	2.5 mg/kg i.p.		Greater labeling in caudate, accumbens, mediofrontal and temporal cortex, amygdala	
c-Fos immunoreactivity	Rat	300 mg/kg i.p.	Amphetamine	5 mg/kg i.p.	Greater labeling in SCN; similar to AMP in ant hypothal, PVN, cAmygdala	Greater labeling in frontal cortex, striatum, habenula, suproptic nuc, blAmygdala	Engber *et al*, 1998a
Glucose utilization by [^{14}C] 2-DG autoradiography	Rat	100, 300 mg/kg i.p.	Amphetamine	5 mg/kg i.p.	↑ 2-DG uptake in 5/46 regions total: cAmygdala, clThal, subic, CA1-CA3, DG	↑ 2-DG uptake in 23/46 regions total: incl frontal cortex, striatum, accumbens, SN, VTA, Subic, CA1-CA3, DG	Engber *et al*, 1998b
Cortical blood flow by laser-Doppler	Rat	300, 600 mg/kg i.p.	Amphetamine	5 mg/kg i.v.	No effect on CBF	↑ CBF	Florence *et al*, 2000
Heart rate, mean arterial blood pressure					Smaller ↑ HR (*vs* AMP); no change MABP	Larger ↑ HR (*vs* Modafinil); ↑ MABP	
Locomotor activity	Mouse	20–40 mg/kg i.p.	Amphetamine	2–4 mg/kg i.p.	↑ Activity similar to AMP	↑ Activity	Simon *et al*, 1994

Table 2 Continued

Experimental measure	Species/preparation	Modafinil dose/ route	Psychostimulant for comparison	Stimulant dose/route	Modafinil effects	Stimulant effects	Reference
Locomotor activity	Mouse	40 mg/kg s.c.	Amphetamine	2 mg/kg s.c.	↑ Activity not blocked by haloperidol; blocked by SCH 23390 only at 30 μg s.c.; ↑ activity in αMPT-treated mice; no reversal of reserpine-induced akinesia	↑ Activity blocked by haloperidol, blocked by SCH 23390 at 7.5–30 μg s.c.; no ↑ activity in αMPT-treated mice; reversed reserpine-induced akinesia	Simon *et al*, 1995
Release of [^{3}H] DA	Mouse Striatal synaptosomes	10 μM	Amphetamine	10 μM	No effect on DA release	↑ DA release	
Extracellular striatal DA by intracranial microdialysis	Orexin-2-receptor knockout narcoleptic dog	5 mg/kg i.v.	Amphetamine	0.1 mg/kg i.v.	↑ DA similar to AMP	↑ DA	Wisor *et al*, 2001
Wakefulness by EEG	DAT knockout mouse	90 mg/kg i.p.	Methamphetamine	2 mg/kg i.p.	↑ Waking abolished in DAT knockout	↑ Waking abolished in DAT knockout	
Wakefulness by EEG	Rat	2.5 mg/kg i.p.	Amphetamine	5 mg/kg i.p.	No rebound ↑ in paradoxical sleep	Rebound ↑ paradoxical sleep	Touret *et al*, 1995
Wakefulness by EEG; locomotor activity	Rat	30, 100, 300 mg/kg i.p.	Methamphetamine	0.5, 1 mg/kg i.p.	No rebound ↑ in paradoxical sleep; smaller effect on locomotor activity	Rebound ↑ paradoxical sleep	Edgar and Seidel, 1997
Wakefulness by EEG; locomotor activity	Rats	Armodafinil 30, 100, 300 mg/kg i.p.	Methamphetamine	1 mg/kg i.p.	Wake-promoting dose comparable to mAMP not assoc with ↑ activity; no acute rebound hypersomnolence	↑ waking and ↑ activity at similar AMP doses; + acute rebound hypersomnolence (↑ NREMS)	Wisor *et al*, 2006
Wakefulness by EEG	Cat	1 mg/kg p.o.	Amphetamine	0.25 mg./kg p.o.	↑ Waking blocked by phentolamine, prazosin, or propranolol, but minimally by haloperidol or αMPT; enhanced by yohimbine	↑ Waking blocked by haloperidol or αMPT but not by phentolamine, prazosin, or propranolol; enhanced by yohimbine	Lin *et al*, 1992
Sleep rebound by EEG	Cat	5 mg/kg p/o/	Amphetamine	1 mg/kg p.o.	No sleep rebound	Sleep rebound: ↑ deep SWS, paradoxical sleep	Lin *et al*, 2000
Waking EEG	Human	300 mg p.o.	Amphetamine	20 mg p.o.	Maintenance of α_1 (8.5–11.5 Hz) power after sleep deprivation	Suppressed power in 0.5–7 Hz bands	Chapotot *et al*, 2003
Locomotor activity	Mouse	32–128 mg/kg i.p.	Amphetamine	2–6 mg/kg i.p.	↑ Activity blocked by prazosin or reserpine, not by sulpiride or αMPT	↑ Activity blocked by sulpiride or αMPT, not by prazosin or reserpine	Rambert *et al*, 1993
			Methylphenidate	16–64 mg/kg i.p.		↑ Activity blocked by sulpiride or resperine, not by prazosin or αMPT	
Locomotor activity	Mouse	40 mg/kg i.p.	Amphetamine	2 mg/kg i.p.	↑ Activity abolished after stress	↑ Activity not abolished after stress	Stone *et al*, 2002b
Stop-signal performance	Rat	3, 10, 30, 100 mg/kg i.p.	Methylphenidate	0.3, 1, 3 mg/kg i.p.	↓ SSRT in rats with slow baseline SSRT only; no effect on Go-trial RT; no effect on cis-flupenthixol-related ↑ GoRT	↓ SSRT in slow rats but ↑ SSRT in fast rats; ↓ go-trial RT in all rats; blocked cis-flupenthixol-related ↑ GoRT	Eagle *et al*, 2007
Executive function and simple reaction time	Humans	400 mg p.o.	Amphetamine	20 mg p.o.	↓ Simple RT, ↑ WCST; no effect on verbal fluency or Stroop interference RT	↓ Simple RT, ↑ WCST; no effect on verbal fluency or Stroop interference RT	Wesensten *et al*, 2005

2007), and it is possible that TA1 receptor activity mediates some of the interactions of modafinil with DA neurons.

Other studies have reported evidence suggesting that modafinil has a mixed profile of effects on central DA systems, and lacks many neurochemical and behavioral effects observed with amphetamine administration. For instance, in contrast to amphetamine, modafinil does not affect the spontaneous release of DA from mouse striatal synaptosomes (Simon *et al*, 1995) or turnover of DA in the mouse caudate nucleus *in vivo* (De Sereville *et al*, 1994); it shows negligible effects on cerebral cortical blood flow (Florence *et al*, 2000), and different patterns of metabolic activation (Engber *et al*, 1998a) and c-Fos induction compared to amphetamine (Engber *et al*, 1998b; Lin *et al*, 1996); it does not produce behavioral stereotypies (Duteil *et al*, 1990; Simon *et al*, 1995) or rebound hypersomnia (Edgar and Seidel, 1997; Lin *et al*, 2000; Touret *et al*, 1995; Willie *et al*, 2005; Wisor *et al*, 2006); it does not significantly alter behavior in the elevated-plus maze (Simon *et al*, 1994); its effect on activity shows stress-induced subsensitivity (which is prevented by corticosterone or dexamethasone pre-treatment) (Stone *et al*, 2002b); pre-treatment with the tyrosine hydroxylase inhibitor α-methyl-para-tyrosine has minimal effects on modafinil-induced increases in arousal in cats (Lin *et al*, 1992) or activity in mice (Duteil *et al*, 1990; Simon *et al*, 1995); its effects on motor inhibitory processes are insensitive to *cis*-flupenthixol (a D1/D2 receptor antagonist) (Eagle *et al*, 2007); and in healthy humans, modafinil has effects on the resting EEG that are distinct from amphetamine (Chapotot *et al*, 2003). Nevertheless, parenteral administration of modafinil does lead to extracellular DA levels (measured by microdialysis) that are increased significantly in the rat prefrontal cortex (PFC) (de Saint Hilaire *et al*, 2001), and in the caudate nucleus of narcoleptic dogs (Wisor *et al*, 2001), although only minimally in the rat hypothalamus (de Saint Hilaire *et al*, 2001). One study found significantly increased extracellular DA in the rat nucleus accumbens, in response to intracerebroventricular modafinil dose of 10 μg (Murillo-Rodriguez *et al*, 2007), whereas another study found only a modest increase in DA in the accumbens after intraperitoneal (i.p.) doses up to 300 mg/kg (Ferraro *et al*, 1997b). Interestingly, in the first study, the modafinil effect on arousal was partly attenuated by the endocannabinoid anandamide. Modafinil effects on midbrain DA neuronal activity remain inconsistently reported. An earlier study found no effects on the activity of mesencephalic DA single units in rats (Akaoka *et al*, 1991), whereas a recent study found that in rat brain slices, modafinil (20 μM) inhibits the activity of ventral tegmental area DA neurons, with this effect abolished by sulpiride, blunted by nomifensine and unaffected by prazosin (Korotkova *et al*, 2006). These latter findings are consistent with modafinil inhibition of DA reuptake, leading to increased activation of the DA cell body autoreceptor to diminish DA cell firing. However, the derived current–voltage relationships for modafinil-evoked *vs* nomifensine-evoked currents showed a very different reversal potential in response to these two agents, suggesting that modafinil may exert its action in this preparation at a site distinct from the DAT. Nevertheless, modafinil effects on wakefulness are abolished in DAT-knockout mice (Wisor *et al*, 2001), although it should be cautioned that D2 autoreceptor function also appears severely impaired in DAT-knockout mice (Jones *et al*, 1999). In a rodent drug discrimination paradigm, modafinil partially generalizes to a cocaine-like stimulus (Gold and Balster, 1996); in addition, modafinil effects on activity in mice are modestly attenuated by the D1 receptor antagonist SCH 23390 (Simon *et al*, 1995), although not by haloperidol (Duteil *et al*, 1990); and the low-activity catechol-*O*-methyl transferase genotype is associated with greater clinical response to modafinil among adults with narcolepsy (Dauvilliers *et al*, 2002). In a study of healthy adults, single-dose modafinil 200 mg caused a reduction in blood prolactin levels; however, unlike the D2/D3 agonist pramipexole, it had no effect on blood growth hormone or thyroid stimulating hormone in these subjects (Samuels *et al*, 2006). Pre-treatment with either the selective catecholamine neurotoxin 6-hydroxy-DA or prazosin also abolishes the modafinil-induced reduction in extracellular gamma amino-butyric acid (GABA) in the neocortex (see below for discussion of effects on GABA) (Tanganelli *et al*, 1994, 1995). There is also evidence for a neuroprotective effect of modafinil on MPTP-induced nigrostriatal DA neuronal toxicity, even with a delayed administration that renders other DAT inhibitors ineffective (Aguirre *et al*, 1999; Fuxe *et al*, 1992). Overall, these findings suggest that modafinil effects on arousal and behavioral activity are at least partly mediated by synaptic DA, but in a manner differing from that of amphetamine, and possibly favoring corticostriatal over subcortical limbic circuits.

Modafinil also has effects on the central NE system. Whereas modafinil does not affect the activity of NE single units in the locus coeruleus (LC) of anaesthetized rats (Akaoka *et al*, 1991), it remains unclear if this is an artifact of anesthesia (see discussion in Souliere *et al*, 2000). Nevertheless, modafinil elevates extracellular NE levels in PFC (along with DA) and rostromedial hypothalamus (de Saint Hilaire *et al*, 2001). It also potentiates the NE-induced inhibition of sleep-promoting neurons in the ventrolateral preoptic nucleus (VLPO), although it has no effect on these neurons in the absence of exogenous NE (Gallopin *et al*, 2004). In addition, pre-treatment with α antagonists prazosin (which acts primarily at α_1, but also has a lower affinity for α_2 receptors (Hieble *et al*, 1995)) or phenoxybenzamine diminishes modafinil-induced increases in arousal (Lin *et al*, 1992) and activity in rats and monkeys (Duteil *et al*, 1990; Hermant *et al*, 1991), as does terazosin pre-treatment or α_{1B} receptor knockouts in mice (Stone *et al*, 2002a). However, modafinil lacks the capacity to reduce cataplexy in dogs or humans with narcolepsy (Billiard *et al*, 1994; Shelton *et al*, 1995), a feature which is similar to other DAT inhibitors, and in contrast to α_{1B} agonists and NET inhibitors (Mignot *et al*, 1993; Nishino *et al*, 1993). In addition, pre-treatment with low doses of the α_2 antagonist yohimbine potentiates modafinil-induced wakefulness (Lin *et al*, 1992) and activity (Duteil *et al*, 1990), whereas higher doses attenuate the activity increases (Duteil *et al*, 1979). This apparent biphasic response to yohimbine suggests that low doses may preferentially block the inhibitory terminal α_2 autoreceptor to enhance NE release and thus augment post-synaptic adrenergic receptor activation by modafinil, whereas higher doses also block post-synaptic α_2 receptors, attenuating modafinil effects.

This phenomenon has also been demonstrated with yohimbine effects on spatial working memory in animal models (Arnsten and Cai, 1993). These findings make it likely that post-synaptic α_2 receptors mediate some of the behavioral effects of modafinil. Importantly, modafinil also augments pupillary dilation parameters (Hou *et al*, 2005) in a manner consistent with LC phasic responses to task-relevant events (Beatty, 1982a, b; Richer and Beatty, 1987), suggesting the potential for LC/NE system effects in optimizing cognitive task performance, as described in the Aston-Jones and Cohen model outlined below (Aston-Jones and Cohen, 2005). Modest attenuation of modafinil-induced arousal and activity has also been observed after pre-treatment with the β-blocker propranolol (Duteil *et al*, 1990; Lin *et al*, 1992). Interestingly, pre-treatment with the NE-selective neurotoxin DSP-4 (which leaves DA neurons intact) does not affect modafinil-induced wakefulness, yet in these NE-lesioned mice both terazosin and the DA autoreceptor agonist quinpirole blunt the modafinil effects (Wisor and Eriksson, 2005).

Taken together, these varied findings suggest that modafinil may potentiate both DA and NE neurotransmission. It appears likely that the elevations in extracellular NE observed after modafinil are responsible for the majority of the adrenergic receptor-mediated effects, which may involve both α_2 and α_1 receptors. D1 and D2 receptors probably also mediate modafinil effects on cognition and behavior. In addition, however, Wisor and Eriksson (2005) have proposed that the elevated synaptic DA resulting from DAT inhibition may lead to DA activation of adrenergic receptors. Despite the common conception that DAT is strictly localized to the striatum (and absent in the frontal cortex), rodents exhibit significant levels of DAT binding in the anterior cingulate, prelimbic, and rostral areas of frontal cortex (Sesack *et al*, 1998; Tassin *et al*, 1978). In post-mortem human brains, DAT is found not only in the striatum, but also throughout the neocortex, including the PFC, albeit at relatively lower concentrations (Ciliax *et al*, 1999). In addition, there is indirect evidence of anatomic and functional convergence of DA and NE systems. For instance, DA and NE share a similar pattern of innervation of the medial PFC in the nonhuman primate (Lewis and Morrison, 1989). There is also indirect evidence that DA can be released from NE neurons in the medial PFC, as there are concomitant elevations of both DA and NE in the medial PFC (as well as occipital cortex) upon LC activation by either direct electrical stimulation or local infusion of α_2 receptor antagonists, whereas both DA and NE are reduced in both cortical areas by local or systemic clonidine (Devoto *et al*, 2001, 2003, 2004a, b; Kawahara *et al*, 2001). There remains the possibility that the enhanced DA results from competition with NE for binding to the NET, which plays an important role in terminating DA action in the cortex (Carboni *et al*, 1990; Moron *et al*, 2002). However, recent evidence suggests that the DA and NE increases in the medial PFC upon LC stimulation are somewhat independent of each other (Devoto *et al*, 2005). Furthermore, a subset of medial PFC neurons are responsive to both neurotransmitters (Bunney and Aghajanian, 1976). DA has an affinity for cloned mouse α_{1B} receptors, which is on the same order of magnitude as NE (Zhang *et al*, 2004), and DA can activate adrenergic receptors in various brain regions (Cornil *et al*, 2002; Crochet and Sakai, 2003; Malenka and Nicoll, 1986). Whereas this evidence is indirect, this suggests a mechanism whereby the modafinil inhibition of DAT inhibition may be related to adrenergic receptor-mediated behavioral effects.

Modafinil Effects on GABA, Glutamate, and Serotonin Systems

Modafinil also has consistent effects on central glutamate and GABA neurotransmitter systems. It increases extracellular glutamate in the thalamus, and at higher doses, in the hippocampus (Ferraro *et al*, 1997a) and striatum (Ferraro *et al*, 1998). It also increases glutamate in the medial preoptic area and posterior hypothalamus, effects which are attenuated by the $GABA_A$ antagonist bicuculline in a dose-dependent manner (Ferraro *et al*, 1999). These regional glutamate effects occur at ascending doses in this order: thalamus = hypothalamus < striatum = hippocampus. Glutamate levels in the globus pallidus and substantia nigra are unchanged after the highest doses administered (Ferraro *et al*, 1998). The effects on glutamate may interact with adrenergic mechanisms, as NE facilitates the synaptic release of glutamate onto medial PFC pyramidal cells, an effect blocked by prazosin but not by yohimbine (Marek and Aghajanian, 1999). These glutamatergic effects do not appear to be due to effects on reuptake (Ferraro *et al*, 1999) or synthesis of glutamate (Perez de la Mora *et al*, 1999). However, there is evidence that modafinil causes increases in the cerebral glutamate–glutamine pool (along with elevations in aspartate and creatine–phosphocreatine, although not in *N*-acetyl aspartate or taurine), as measured by 2D COSY ^{1}H-NMR (Pierard *et al*, 1995). This increase in the glutamate–glutamine pool may result from increased glutamine synthetase activity, as the mRNA content of this enzyme is increased after modafinil (Touret *et al*, 1994).

Modafinil also causes a dose-dependent decrease in GABA in the cortex (Tanganelli *et al*, 1994, 1992, 1995), the medial preoptic area and posterior hypothalamus (Ferraro *et al*, 1999, 1996), striatum, and globus pallidus (Ferraro *et al*, 1998), and at higher doses, in the hippocampus (Ferraro *et al*, 1997a), thalamus (Ferraro *et al*, 1997a), substantia nigra (Ferraro *et al*, 1998), and nucleus accumbens (Ferraro *et al*, 1997b). These regional GABA effects occur at ascending doses in this order: cortex < striatum/pallidum = hypothalamus < thalamus = hippocampus = substantia nigra = nucleus accumbens. In addition, in comparison to a single parenteral dose of modafinil, a 7-day course of parenteral administration leads to reductions of cortical GABA that are equal in magnitude but shorter-lasting (Tanganelli *et al*, 1994). Modafinil does not appear to directly affect the synthesis (Perez de la Mora *et al*, 1999; Tanganelli *et al*, 1995), basal or K^+-evoked release, or uptake of GABA (Antonelli *et al*, 1998; Tanganelli *et al*, 1995). Interestingly, modafinil does prevent the effect of glutamate cytotoxicity on reduction of GABA release from cultured cortical neurons (Antonelli *et al*, 1998).

The effects on extracellular GABA appear to be mediated by modafinil effects on other neurotransmitter systems. Cortical GABA effects require intact catecholamine neurons, as pre-treatment with 6-hydroxy DA abolishes modafinil-induced reductions in GABA (Tanganelli *et al*, 1994), as does prazosin (Tanganelli *et al*, 1995). Modafinil effects on

GABA are also influenced by the serotonin system (5HT). Modafinil-induced reductions in GABA are abolished in the cortex by pre-treatment with $5HT_2$ receptor antagonists methysergide or ketanserin (Tanganelli *et al*, 1992), and in the hypothalamus by the $5HT_3$ antagonist MDL72222 (which alone has no effect on GABA levels) (Ferraro *et al*, 1996). In addition, the 5HT-selective neurotoxin 5,7-dihydroxytryptamine reverses modafinil-induced reductions in cortical GABA (Tanganelli *et al*, 1995). Modafinil causes elevations in extracellular 5HT that are significant and dose-dependent in the frontal cortex, central nucleus of the amygdala, and dorsal raphe nucleus, but minimal in the hypothalamus (de Saint Hilaire *et al*, 2001; Ferraro *et al*, 2000, 2002). In addition, modafinil and the 5HT reuptake inhibitors fluoxetine, paroxetine, and imipramine mutually enhance the effect of each other on elevations in cortical 5HT (Ferraro *et al*, 2000, 2005). These studies all used microdialysis to measure extracellular 5HT and GABA. In addition, in frontal cortical slices, modafinil increases electrically evoked (but not spontaneous) 5HT efflux in a concentration-dependent manner (Ferraro *et al*, 2000, 2001), whereas neither type of 5HT efflux is affected by modafinil in cortical synaptosomes, in contrast to fenfluramine, which enhances both types of 5HT efflux in both cortical preparations (Ferraro *et al*, 2000, 2001). Taken together, this literature suggests that modafinil effects on GABA are at least partly mediated by 5HT, which do not involve direct effects on synthesis or vesicular storage of 5HT. Given that α receptors are found in high concentrations in the dorsal raphe nucleus and exert a tonic excitatory influence on raphe 5HT cell bodies (Millan *et al*, 2000), the modafinil effects on GABA may be mediated by adrenergic effects on 5HT activity.

Modafinil Effects on Orexin, Histamine, and Acetylcholine Systems

The clinical efficacy of modafinil in narcolepsy, a condition characterized by a severe deficiency of orexin (hypocretin) in the brain (Nishino, 2003), suggests that modafinil may have clinically relevant effects on this neurochemical system. Modafinil does increase Fos-immunoreactivity in identified orexin cells in the perifornical area of mice and rats (Chemelli *et al*, 1999; Scammell *et al*, 2000). However, modafinil induces wakefulness more potently in orexin-knockout mice than in wild-type mice, with similar patterns of Fos-immunoreactivity (Willie *et al*, 2005). In addition, modafinil does not bind the orexin 1 receptor (Wieland *et al*, 2002) and retains effects on both extracellular striatal DA and wake-promoting activity in orexin 2 receptor-deficient narcoleptic dogs (Wisor *et al*, 2001). Therefore, modafinil effects on arousal do not appear to be mediated through the orexin system, and the precise role of orexin in the cognitive and clinical effects of modafinil remains unknown. Modafinil also activates Fos in the tuberomammillary nucleus (TMN), which contains wake-promoting histaminergic (HA) neurons (Scammell *et al*, 2000), and both i.p. and intracerebroventricular modafinil elevates extracellular HA in the anterior hypothalamus (Ishizuka *et al*, 2003). However, direct injection of modafinil into the TMN does not affect HA release (Ishizuka *et al*, 2003). In addition, whereas HA neurons of the hypothalamus project widely throughout the brain (as do orexinergic neurons), they also receive significant innervation from brainstem serotonergic and catecholamine nuclei (primarily outside the LC and VTA), and the inhibition of HA neurons in the TMN during sleep is mainly due to GABAergic innervation from the VLPO (Haas and Panula, 2003). Interestingly, despite the close interaction between central HA and acetylcholine systems (Blandina *et al*, 2004), modafinil does not appear to affect extracellular acetylcholine in the cortex (Tanganelli *et al*, 1992) and does not reverse the scopolamine-induced increase in omission errors on the 5-choice serial reaction time (RT) test, in contrast to physostigmine (Waters *et al*, 2005). Given the multiple effects on catecholamines, 5HT and GABA described above for modafinil, it appears likely that modafinil effects on HA are mediated by one or more of these neurotransmitter systems. Nevertheless, a role for HA in a range of learning and memory paradigms is now established, with apparent opposing effects of H_1 and H_3 receptor activation, both of which may exert cognitive effects in interaction with cortical acetylcholine (Passani *et al*, 2000). It is intriguing to consider that some of the cognitive effects of modafinil may be mediated by enhancement of cortical HA effects.

Summary of Neurochemical Effects of Modafinil

In summary, modafinil is a psychostimulant that differs from amphetamine in structure, neurochemical profile, and behavioral effects. To date, the only central neurotransmitter elements to which modafinil has been demonstrated to directly bind are the DAT and NET, which it inhibits at modest potency. However, at doses used in clinical settings, modafinil may exert a significant inhibition of both catecholamine transporters. In addition, modafinil administration leads to significantly elevated extracellular DA, NE, 5HT, glutamate, and HA levels, and decreased GABA levels. These effects are particularly prominent in the neocortex, and generally less potent or minimal in various subcortical areas. The effects on DA and NE appear to be primary; effects on 5HT, GABA, glutamate, orexin, and HA may be secondary to catecholamine effects. The arousal and activity-promoting effects of modafinil are largely a function of activity in catecholamine systems, with α and β adrenergic receptors implicated and DA receptors also implicated but yet to be fully studied. Both the elevations in extracellular monoamines (including 5HT) measured by microdialysis and the effects on waking and activity mediated by catecholamines are generally observed with parenteral doses of 100 mg/kg or less. In contrast, the effects on extracellular glutamate and GABA (with the exception in the hypothalamus) generally require higher doses. Taken together, these sources of evidence suggest that the cognitive and behavioral effects seen in clinical use of modafinil are likely to be a function primarily of changes in monoamine activity rather than glutamate or GABA.

EFFECTS ON COGNITION AND NEUROBIOLOGICAL MEASURES OF INFORMATION PROCESSING

Modafinil Effects in Animal Models of Cognition

A number of studies of cognition in animal models have indicated the efficacy of modafinil for cognition (Table 3).

Pre-treatment with modafinil is associated with a dose- and delay-dependent enhancement of working memory performance on a sequential alternation task in mice, without affecting exploratory or anxiety-related activity (Beracochea *et al*, 2001). Modafinil also dose-dependently improves the rate of spontaneous alternation as a measure of working memory performance in mice (Pierard *et al*, 2006). Interestingly, the optimal dose for enhancing working memory under stress conditions (immobilization or light exposure) was lower (8 mg/kg) than that under non-stress conditions (16 mg/kg); and at these doses, plasma corticosterone levels were lowered with stress (and inversely correlated with working memory performance), yet were elevated in the absence of stress. In another study of working memory, modafinil enhanced performance of rats on a delayed nonmatching to position task, which was not accounted for by the increased activity seen in the animals at the higher doses (Ward *et al*, 2004). It also dose-dependently improves performance of mice on a serial reversal discrimination task (Beracochea *et al*, 2003). This task requires mice to use current cues to rapidly adopt a context-appropriate strategy to make correct responses, and this learning curve is sensitive to damage to either the anterior cingulate (but not posterior cingulate) cortex or the mediodorsal nucleus of the thalamus (Krazem *et al*, 1995; Meunier *et al*, 1991). The anterior cingulate cortex is also an area which shows c-Fos activation after modafinil (Scammell *et al*, 2000). Interestingly, daily administration of modafinil (at the same dose) during learning acquisition of this task is associated with a more rapid and higher level of learning than after a single dose, whereas showing no effect on intersession perseveration or general alternation ability (Beracochea *et al*, 2002). This suggests a specific enhancement of the adoption of a context-dependent strategy, and also suggests that this effect is positively related to duration of treatment. Another study tested the effects on visual discrimination and visual sustained attention of oral doses of modafinil, from 8 to 64 mg/kg, administered to middle-aged female rats (Morgan *et al*, 2007). These investigators found no modafinil effects on visual discrimination learning, but did observe a dose- and delay-dependent effect on sustained attention, manifest as increased accuracy and speed and decreased premature responses. In this task, no modafinil effects were evident on omission errors, or measures of motivation or motor activity. In contrast, a study where rats performed the 5-choice serial RT task, modafinil in general did not appear to have effects on attention measures, as well as measures of sensorimotor and inhibitory processes (Waters *et al*, 2005). However, a recent report of modafinil effects on the Stop-Signal Reaction Time (SSRT) task may resolve these discrepant findings (Eagle *et al*, 2007). In this study, modafinil significantly decreased (ie, improved) SSRT only in those rats who exhibited relatively longer (ie, impaired) SSRT at baseline. This effect was apparent at 10 and 30 mg/kg i.p. but not at 3 mg/kg. In addition, no effects of modafinil were found on go-trial RT, and at the highest modafinil dose tested (100 mg/kg), modafinil was associated with a decrement in go-trial accuracy. These findings suggest that modafinil (at doses up to 30 mg/kg) affects the speed of the stop process rather than attention or response selection; yet at higher doses, these latter processes are affected adversely. Furthermore, in this study, *cis*-flupenthixol (a D1/D2 receptor antagonist) was co-administered with modafinil in a second set of experiments to test the role of D1/D2 receptors in mediating modafinil effects. Here, *cis*-flupenthixol (at doses of 0.01 or 0.04 mg/kg i.p.) showed no effect on the modafinil-mediated decrease in SSRT, or when administered alone. Conversely, modafinil (at 10 mg/kg) failed to antagonize the *cis*-flupenthixol-mediated increase in go-trial RT, in contrast to methylphenidate 1 mg/kg, which did block this effect of *cis*-flupenthixol. These results suggest that D1 or D2 receptors do not mediate the effects of modafinil on inhibitory processes as measured in this task.

Modafinil Effects on Cognition in Healthy Non-Sleep-Deprived Adults

Modafinil appears to enhance cognitive performance in healthy adults who are not sleep-deprived (Table 3). In one randomized, placebo-controlled single-dose study of 60 adults, modafinil improved performance on digit span, visual recognition memory, spatial planning, and SSRT, suggesting improved working memory and inhibition of pre-potent responding (Turner *et al*, 2003). No differences were found between the 100 and 200 mg single doses. Other studies have found delay-dependent improvements in working memory, such as on maintenance and manipulation and delayed matching tasks, without a speed-accuracy trade-off, or effects on attention tasks (Muller *et al*, 2004); and on vigilance, but not perceptual, arithmetic, or reasoning performance (Baranski *et al*, 2004). A different research group has found a single dose of modafinil 100 mg to improve performance on digit span and a sustained attention task (Randall *et al*, 2005b), yet failed to find significant improvement on a range of other cognitive tests with single doses of 100 or 200 mg modafinil in this and other studies. However, this group has studied university students who appear to have a high IQ (average of 115 in one study), with likely general ceiling effects on performance (Randall *et al*, 2003, 2005a). Indeed, a retrospective analysis of the studies of students found modafinil effects on cognition only for a subgroup with relatively lower IQ (Randall *et al*, 2005a). In another study (Randall *et al*, 2004), a group of relatively older subjects (aged 50–67) was studied, which may include individuals with age-related decline that involves neurochemical systems unaffected by modafinil, such as acetylcholine (Tanganelli *et al*, 1992).

Modafinil Effects on Cognition in Healthy Sleep-Deprived Adults

Several studies of modafinil effects on cognition in healthy adults undergoing sleep deprivation or simulated night shifts have been reported (see (Wesensten, 2006) for review). One study of adults with 85 h of sleep deprivation found single-dose modafinil 400 mg to reduce errors on the Wisconsin Card Sort Test (WCST) and interference on the Stroop (compared to placebo), and comparable to 600 mg caffeine and 20 mg amphetamine (Wesensten *et al*, 2005). Another study from this research group found minimal effects of modafinil single-dose (100, 200, or 400 mg) on measures of RT or arithmetic performance (Wesensten

Table 3 Effects of Modafinil on Cognition and Other Information-Processing Measures

Measure	Subject sample	*N*	Dose/route/design	Positive effects on performance	Lack of effect	Reference
Delayed spontaneous alternation (SA)	Mouse	8/grp	8, 32, 64 mg/kg i.p.	↑ Alternation score with delay-dependent effect (60, 180 s ITI)	Alternation score at 5 s ITI	Beracochea *et al*, 2001
Serial spatial discrimination reversal	Mouse	10/grp	32, 64 mg/kg i.p. qd for 5 d	Faster emergence of win-stay rule (learning rate) at 64 mg/kg (not at 32 mg/kg)	Day 1 Acquisition rate; forgetting rates; contingently reinforced alternation rates over 5 d	Beracochea *et al*, 2002
Serial spatial discrimination reversal	Mouse	10/grp	32, 64 mg/kg i.p. qd for 5 d	Faster emergence of win-stay rule (learning rate) at 64 mg/kg (not at 32 mg/kg) on day 5	Day 1 Acquisition rate; forgetting rates; contingently reinforced alternation rates over 5 d	Beracochea *et al*, 2003
Delayed spontaneous alternation (SA)	Mouse		0, 8, 16, 32 mg/kg i.p. ± chronic stress for 14 d	Non-stress condition: ↑ alternation rate optimal at 16 mg/kg; stress condition: ↑ alternation rate optimal at 8 mg/kg	Non-stress task completion time	Pierard *et al*, 2006
Delayed non-match to position in water maze	Rat	40	0, 30, 55, 100 mg/kg i.p. qd for 10 days	↑ Accuracy days 5–8 (55 mg/kg) and days 6–8 (100 mg/kg); ↑% reaching criterion (80%) qd	Performance at 30 mg/kg	Ward *et al*, 2004
Cognitive battery	Rat		0, 8, 32, 64 mg/kg i.p.	↑ Accuracy, ↓RT and ↓ premature responses on 3-choice visual attention task with long delay at 64 mg/kg only	Visual discrimination performance; omission errors or measures of motivation or motor activity	Morgan *et al*, 2007
5-Choice serial RT	Rat	64	32, 64, 128 mg/kg p.o.	↑ Premature responding in reduced stimulus duration or duration/intensity	5-CSRT accuracy in standard conditions or with altered stimulus	Waters *et al*, 2005
Stop signal task	Rat	30	0, 3, 10, 30, 100 mg/kg i.p.	↓ SSRT only in rats with slow baseline SSRT; not reversed by cis-flupenthixol 0.01 or 0.04 mg/kg	SSRT in fast rats; Go-RT; no effect on cis-flupenthixol (0.04 mg/kg)-induced ↑ Go-RT; SSRT and Go-RT effects different from d-AMP	Eagle *et al*, 2007
Visuospatial DMS; digit maintenance manipulation	Healthy adults	16	200 mg p.o. double-blind, placebo-controlled within-subjects	↑ Accuracy DMS long-delay and manipulation	Simple digit maintenance; letter-cancellation, Trail-making task	Muller *et al*, 2004
CANTAB battery and other tasks	Healthy adults	60	0, 100, 200 mg p.o.	↑ Accuracy Digit Span (forward and backward), pattern recognition memory, Tower of London, Stop Signal, ↓RT DMS and Stop Signal	Accuracy visuospatial paired assoc learning, Spatial WM, Spatial Span, ID/ED, digit sustained attention, Gambling	Turner *et al*, 2003
Cognitive battery	Healthy adults	18	4 mg/kg p.o. double-blind, placebo-controlled within-subjects	Serial RT, logical reasoning, 1-Back	Addition, line discrimination, confidence judgments	Baranski *et al*, 2004
Somatosensory evoked potentials (median nerve stimulation)	Healthy adults	6	100 mg p.o.	↑ 500–700 Hz oscillation (12–18 ms latency burst) over frontal, central and parietal areas; source-localized to subcortical	2nd burst (18–28 ms latency) 500–700 Hz oscillations	Della Marca *et al*, 2004
CANTAB and other cognitive tasks	Healthy adults	60	0, 100, 200 mg p.o. parallel groups	↓RT Stroop color-naming, ↑ accuracy digit sustained attention (200 mg); ↑ digit span forward and backward (100 mg)	Spatial working memory, Logical memory, PASAT, symbol copy, digit cancellation, verbal fluency, ID/ED, Trails A,B	Randall *et al*, 2005b
CANTAB and other cognitive tasks	Healthy adults; high IQ	30	0, 100, 200 mg p.o.	No significant effects	ID/ED, DMS, spatial planning, digit sustained attention, logical memory, Stroop, Trails A, B, verbal fluency, clock-drawing	Randall *et al*, 2003
CANTAB cognitive	Healthy adults;	45	0, 100, 200 mg p.o. parallel groups	↓RT Stroop color-naming, ↑ accuracy	Visual DMS, Spatial Planning, digit	Randall *et al*, 2004

Table 3 Continued

Measure	Subject sample	N	Dose/route/design	Positive effects on performance	Lack of effect	Reference
battery	relatively older			Clock-Drawing; ↓ total accuracy ID/ED (all at 200 mg)	sustained attention, logical memory, Stroop, Trails A, B, verbal fluency	
Cognitive battery	Sleep-deprived healthy adults	48	400 mg p.o. parallel groups	↓ Simple RT, ↑ accuracy WCST; ↓% impaired on Biber Cognitive Estimation	Stroop, verbal fluency; simple RT and WCST comparable to Caffeine 600 mg, d-AMP 20 mg	Wesensten *et al*, 2005
Cognitive battery	Sleep-deprived healthy adults	50	0, 100, 200, 400 mg p.o. parallel groups	Reversed slowing in simple RT, 10-choice RT, 4-choice RT	10-, 4-choiceaccuracy; serial addition/ subtraction; modafinil (200, 400 mg) effects on RT comparable to caffeine 600 mg	Wesensten *et al*, 2002
Cognitive battery	Sleep-deprived healthy military recruits	41	300 mg p.o. for 3 days	↓ Simple RT, ↑ accuracy on short-term memory, logical reasoning	NA	Pigeau *et al*, 1995
AX-CPT, coding task (similar to digit symbol)	Sleep-deprived healthy ER physicians	25	200 mg p.o. double-blind, within-subjects counterbalanced	↑ AX accuracy with long (5 s) ISI; ↑ AY accuracy with short (1 s) ISI	AX or BX accuracy at 1 s ISI; AY or BX accuracy at 5 s ISI; no effect on coding task	Gill *et al*, 2006
Cognitive battery	Healthy adults in simulated night-shift	32	200 mg p.o. qd for 4 days	↑ Accuracy visual sustained attention, WCST, Hayling Sentence Completion, Verbal flexibility	Accuracy on Digit Symbol, Letter-Number Sequencing, verbal association	Walsh *et al*, 2004
Cognitive battery	Healthy adults in simulated night-shift	11	200, 400 mg p.o. qd; placebo-controlled within-subjects counterbalanced over 23 days	↓ False alarms on divided attention; ↑ accuracy on immediate digit recall; ↑ accuracy digit symbol; ↑ sequence learning; ↑ sustained attention (all at both doses)	NA	Hart *et al*, 2006
fMRI with N-back	Sleep-deprived healthy adults	8	200 mg p.o. double-blind, placebo-controlled	↓RT on 2-Back only associated with extensive cortical activation	RT on 1-Back and 3-Back	Thomas and Kwong, 2006
Flight simulator	Sleep-deprived healthy adults		200 mg p.o. within-subject counterbalanced	Attenuated decline in performance after sustained waking	Effects comparable to 200 mg caffeine	Dagan, 2006
fMRI with passive response to auditory and visual stimuli	Narcolepsy patients and Healthy controls	12 12	400 mg p.o. *vs* placebo parallel-groups within-Dx	Spatial extent of activation inversely correlated with baseline extent $r=-0.76$	No group effects on visual or auditory cortex activation	Ellis *et al*, 1999
Cognitive battery	Narcolepsy patients	64 67 65	Armodafinil 0, 150, 250 mg p.o. qd for 12 weeks; double-blind, placebo-controlled	↑ score composite of RT on simple RT, choice RT, digit vigilance, at 150 mg and combined 150/250 mg groups; ↑ score composite of 4 recall/recog tasks (both doses); ↑ score composite of RT on WM and recog memory tasks (250 mg and combined dose groups)	Non-sig ↑ score composite of accuracy on choice RT and digit vigilance	Harsh *et al*, 2006
Arithmetic (Pauli Test) and visual/auditory divided attention	Narcolepsy patients medication-free	15	400 mg p.o. *vs* placebo for 3 weeks; double-blind crossover	↑ # correct calculations; # correct inversely correlated with power in delta (peak $r=-0.45$ ACC), theta (peak $r=-0.65$ medFG), slow alpha (peak $r=-0.55$ in medFG) by EEG-LORETA, esp left frontal cortex	Visual/auditory divided attention RT	Saletu *et al*, 2007

Table 3 Continued

Measure	Subject sample	*N*	Dose/route/design	Positive effects on performance	Lack of effect	Reference
P300 by scalp EEG	Narcolepsy patients	21	0, 200, 400 mg p.o.	Clinical responders: ↓ latency auditory and visual P300 and ↑ amplitude auditory and visual P300	RT on auditory, visual tasks	Sangal *et al*, 1999b
Wisconsin card sort test	Narcolepsy patients	24	400 mg p.o. qd or 300 mg p.o. bid, *vs* placebo, for 3 weeks; double-blind	↓ Errors	NA	Schwartz *et al*, 2004
P300 during visual or auditory oddball, PASAT	Multiple sclerosis patients	33	100 mg p.o. qd for 4 weeks open-label	NA	No correlation between clinical response and P300 or PASAT score	Nagels *et al*, 2007
CANTAB battery, digit span and stop task	Schizophrenia patients	20	200 mg p.o.	↑ Accuracy Digit Span (forward and backward), delayed pattern recognition memory, ID/ED (ED errors), Tower of London	Immediate pattern reco memory, DMS, Spatial WM, Spatial Span, Stop Signal RT, Go-RT	Turner *et al*, 2004b
Letter-number sequencing	Schizophrenia patients	11	100 mg p.o. qd days 1–14 then 200 mg p.o. qd open-label	↑ Performance on LNS	NA	Rosenthal and Bryant, 2004
fMRI with N-Back	Schizophrenia patients	17	100 mg p.o. *vs* placebo; double-blind within-subjects	↑ Activation in bilateral DLPFC, IPL, right posterior parietal and ACC in 2- *vs* 0-Back	Accuracy on 2-Back at chance for both modafinil and placebo conditions; no effect on 0-Back	Spence *et al*, 2005
fMRI with task demand of aperiodic motor variation (SAINT)	Schizophrenia patients	12	100 mg p.o. *vs* placebo; double-blind within-subjects	↑ Bilateral DLPFC (BA 46) activation; left BA 46 correlated $r = 0.65$ with coefficient of variation; neg correlated with baseline verbal fluency	NA	Hunter *et al*, 2006
Cognitive battery	Schizophrenia patients	13 *vs* 11	200 mg p.o. qd *vs* placebo for 8 weeks	No significant effects on cognition between groups	CPT-IP, ODR, DMS, RAVLT, letter-number span	Sevy *et al*, 2005
Cognitive battery	Schizophrenia patients	20	200 mg p.o. qd for 8 weeks; double-blind, placebo-controlled	No significant effects on cognition between groups	CVLT, Degraded-Stim CPT, Trails B	Pierre *et al*, 2005
Cognitive battery	Major depression patients	33	Flexible add-on dosing 100–400 mg p.o. qd for 4 weeks (mean 275 mg/day)	↓ Stroop interference	Letter-Number Sequencing, Digit Span forward and backward, Trails A,B	DeBattista *et al*, 2004
CANTAB and stop-signal task	ADHD patients	20	200 mg p.o. double-blind placebo-controlled	↑ Accuracy Digit Span (forward and backward), delayed pattern recognition memory, DMS, Tower of London; ↓ Stop Signal RT	Accuracy Immediate pattern recog memory, visuospatial paired assoc learning, spatial WM, Spatial Span, visual sustained attention, ID/ED, Go-RT	Turner *et al*, 2004a
Cognitive battery	Adult ADHD patients	22	Double-blind, placebo-controlled crossover (mean dose 207 mg/day)	Trend ↑ verbal fluency	Stroop, Digit Span	Taylor and Russo, 2000
Test of variables of attention	ADHD patients	24	Flexible dose, 200–300 mg p.o. qd (mean 264 mg) for 5–6 weeks	↑ TOVA ADHD *z* score (improved)	NA	Rugino and Copley, 2001
Test of variables of attention	ADHD patients	11	Flexible dose, 100–400 mg p.o. qd (mean 195 mg) for 2–7 weeks (mean 4.6)	↑ TOVA ADHD score, including impulsivity and inattention subscores (improved)	NA	Rugino and Samsock, 2003
Test of variables of attention	ADHD patients	200	Double-blind, flexible dose 85–425 mg p.o. qd (mean 361 mg) for 2–56 days (mean 31.5 d)	↑ TOVA ADHD score at final visit, incl inattention subscore	TOVA commission errors	Greenhill *et al*, 2006

et al, 2002), suggesting that the improvement in executive functions found in their other study was not merely due to enhanced speed of response. A study of 41 military recruits, who received modafinil 300 mg, d-amphetamine 20 mg, or placebo on three separate occasions of 64 h of continuous work, found both medication treatment groups to perform better than the placebo group on short-term memory, logical reasoning, and RT measures (Pigeau *et al*, 1995). A double-blind, placebo-controlled study of emergency department physicians participating after an overnight work shift found single-dose modafinil 200 mg to improve accuracy (relative to placebo) on both AX and AY conditions of the AX-CPT task (Gill *et al*, 2006). One study of healthy adults undergoing simulated night-shift work found a 4-day regimen of modafinil 200 mg to reduce errors (compared to placebo) on the WCST and the Hayling Sentence Completion Test (Walsh *et al*, 2004), which requires cognitive control and is associated with activation of dorsolateral PFC (Nathaniel-James and Frith, 2002) and anterior cingulate cortex (Nathaniel-James *et al*, 1997) measured by fMRI. Another double-blind, placebo-controlled study of healthy adults undergoing simulated day- and night-shift conditions found a 3-day course of modafinil 200 or 400 mg to improve performance on divided attention, immediate recall, and a version of the digit-symbol task, relative to placebo (Hart *et al*, 2006). Modafinil effects were generally as strong at the 200 as the 400 mg dose, with stronger effects during the night-shift than day-shift condition. A randomized, placebo-controlled fMRI study of single-dose modafinil 200 mg after overnight sleep deprivation in eight healthy men found this treatment to improve working memory performance and associated cortical activation under intermediate working memory loads, using the N-Back (Thomas and Kwong, 2006).

Modafinil Effects on Cognition and Brain Function in Clinical Populations

A few studies of cognition and functional neuroanatomy have been conducted in patients with narcolepsy (Table 3). An fMRI study of narcolepsy patients and healthy controls found no within- or between-group differences in modafinil *vs* placebo effects on extent of activation across the whole brain in passive response to combined visual and auditory stimulation (Ellis *et al*, 1999). This suggests that modafinil does not merely cause diffuse activation across the cortex, as might result from primary effects on arousal or early sensory processes. A multicenter randomized, double-blind placebo-controlled 12-week study of armodafinil effects in 196 narcolepsy patients included one group receiving 150 mg/day, and another group receiving 250 mg/day. This study found armodafinil to be associated with several effects on cognition: on a summary RT measure from 3 RT tests, the low-dose and pooled low/high-dose groups performed significantly faster than the placebo group at the final (week 12) assessment; on a measure of overall accuracy across four episodic recall and recognition tasks, each armodafinil-treated group performed significantly better than placebo at 4 weeks with this difference maintained throughout the remainder of the study; and the high-dose and pooled-dose groups were significantly faster on an RT measure derived from the working memory and episodic recognition memory tasks (Harsh *et al*, 2006). Other studies have examined effects on scalp electrophysiology measures in narcolepsy patients. A 3-week treatment with modafinil 400 mg/day remediated the decrement in α-2 and β-1–3 power in a vigilance-controlled EEG (measured by low-resolution brain electromagnetic tomography, LORETA) that was observed in placebo-treated patients with narcolepsy; in this sample, modafinil treatment was also associated with decreases in power in the θ and δ bands in the resting EEG (Saletu *et al*, 2004). The remediating effects on α and β power were localized to several cortical regions, including frontal and cingulate cortex. In a related study, this group found that modafinil treatment of medication-free narcolepsy patients (titrated from 100–400 mg/day over 3 weeks) was associated with significantly improved performance on a test of simple arithmetic (Pauli Test) and effects on the EEG (by LORETA) similar to those found in the earlier study (Saletu *et al*, 2007). Furthermore, Pauli Test performance was correlated with modafinil effects on *decreased* θ and δ power, and these correlations were particularly localized to the frontal and anterior cingulate cortices. In addition, among narcolepsy patients, who exhibit a prolonged auditory and visual P300 latency (Sangal *et al*, 1999a), a relatively shorter P300 latency was associated with clinical response to modafinil (at either 200 or 400 mg/day), using a measure of daytime sleepiness (Sangal *et al*, 1999b). A shorter auditory P300 latency was also associated with remediation of fatigue in patients with multiple sclerosis in response to 4 weeks of modafinil 100 mg/day (Nagels *et al*, 2007). A study of scalp somatosensory evoked potentials in healthy adults found specific effects of modafinil 100 mg single dose on the short-latency component of high-frequency (500–700 Hz) oscillations, with a wide scalp distribution over the scalp and uniform polarity, and dipole modeling suggesting a subcortical source likely to be located in the brainstem (Della Marca *et al*, 2004). Whereas it is not entirely certain how to resolve this finding with the reported effects on the other EEG phenomena, it is possible that this last effect represents activation of brainstem centers with a diffuse cortical distribution, such as the monoamine nuclei, whose activity may be associated with widespread effects on other cortical electrical phenomena such as the other frequency bands. This issue may be best resolved by testing modafinil effects either in animal models, where single-unit or multiunit activity can be compared to simultaneous scalp electrical activity, or in humans with both scalp EEG and whole-brain imaging by fMRI.

Modafinil effects on cognition have been studied as well in psychiatric populations (Table 3). This includes a study of 20 patients with stable chronic schizophrenia, in a double-blind, placebo controlled, single-dose crossover study (Turner *et al*, 2004b). In this study, the modafinil 200 mg dose (added to concurrent atypical antipsychotic medications) was associated with significantly improved performance (relative to placebo) on digit span (forwards and backwards) and trends toward better performance on delayed visual recognition memory and a version of the Tower of London. In addition, on modafinil, these patients made fewer extradimensional shift errors on the intra-dimensional/extradimensional shift (ID/ED) task. In this visual discrimination learning task (developed as a WCST

analog that could be performed by animals), the ED shift is a form of attentional set-shifting mediated by fronto-cortical loops that are modulated by ascending DA systems. Interestingly, ID/ED performance enhancement was not observed by the same group in similarly-designed studies of modafinil in patients with ADHD (Turner *et al*, 2004a) or healthy adults (Turner *et al*, 2003), who showed a pattern of performance improvement similar to each other (see below), but different from the patients in the schizophrenia study. This suggests a measure of specificity to patients with schizophrenia for enhancement of attentional set-shifting, a function strongly dependent in this task on lateral PFC (Dias *et al*, 1996). Modafinil had no effect on SSRT in these patients, which may be due to a higher dosage threshold for SSRT effects, as decreased SSRT was seen in healthy rats performing this task only at higher doses (10 and 30 mg/kg i.p., but not at 3 mg/kg, a dose very comparable to the 200 mg oral dose used with the schizophrenia patients) (Eagle *et al*, 2007). An open-label study of 11 chronic schizophrenia patients found add-on modafinil (titrated from 100 mg/day on days 1–14 to 200 mg/day on days 15–28) to improve performance on letter-number sequencing (Rosenthal and Bryant, 2004). In a double-blind, placebo-controlled study of 17 schizophrenia patients, modafinil 100 mg single-dose was associated with greater activation of the dorsal anterior cingulate cortex during performance of an N-back Task (Spence *et al*, 2005). In another double-blind, placebo-controlled fMRI study of 12 schizophrenia patients with prominent negative symptoms (a subset of the sample in Spence *et al*, 2005), this research group found modafinil 100 mg single-dose to be associated with increased bilateral dorsolateral PFC activity (Brodmann's areas 9 and 46) during performance of a task requiring subjects to press a button in an aperiodic manner (Hunter *et al*, 2006). Left BA 46 activity was significantly associated with the temporal variation in interresponse intervals ('coefficient of variation'), the primary measure of task performance. The placebo-condition coefficient of variation was negatively associated with changes in both this behavioral measure and BA 46 neural activity, suggesting that those patients with worse baseline performance exhibited the strongest response to modafinil. This group has also reported that after a single modafinil dose of 100 mg, schizophrenia patients exhibited a significantly greater amount of behavioral activity than placebo-treated patients, measured with wrist-worn actigraphy over a 20-h period on an inpatient research unit (Farrow *et al*, 2006). Two studies of add-on modafinil treatment of schizophrenia patients have failed to find significant differences from placebo on behavioral cognitive measures. In the first, 20 clinically stable but moderate to severely ill (Clinical Global Impression scale (CGI) $\geqslant 4$) chronic schizophrenia patients performed the following tasks at baseline and again after 8 weeks of double-blind add-on modafinil, with doses of 100 or 200 mg/day: CPT-Identical Pairs version, Letter-Number Span, oculomotor delayed response, delayed match-to-sample, verbal (letter) fluency, and the Rey Auditory Verbal Learning Test (Sevy *et al*, 2005). On the CPT-IP, the effect size (Cohen's *d*) from baseline to week 8 within the modafinil group was approximately 0.3 for a few measures, whereas within the placebo group, it was approximately 0.1. On the Letter-Number Span, within the modafinil group, *d* was approximately 0.5 *vs* −0.5 within the placebo group. These results suggest that the small sample sizes (10 patients completing the study in each group) conferred inadequate statistical power to detect between-group differences on these measures. In addition, the modafinil group was relatively worse in performance at baseline on most of the other cognitive measures, whereas the placebo group exhibited a significant response on the clinical measures. In the second study (available only as an abstract), a total of 20 patients were enrolled, with no significant effects of 8-week modafinil 200 mg/day found on the California Verbal Learning Test, Degraded-Stimulus Continuous Performance Test, or Trails Part B (Pierre *et al*, 2005). The abstract does not indicate how many subjects completed the study. These studies appear to remain inconclusive regarding null findings with modafinil on cognitive dysfunction in schizophrenia and provide emphasis on the critical need for adequate statistical power in clinical trials study design.

In a study of patients with major depression (with 31 completers), modafinil improved another prefrontal-dependent measure, Stroop interference, in a 4-week open-label trial with flexible dosing between 100 and 400 mg/day added to existing antidepressant medications (DeBattista *et al*, 2004). In a double-blind 3-week trial comparing 400 *vs* 600 mg/day in 24 patients with narcolepsy, modafinil reduced errors on the WCST (Schwartz *et al*, 2004). The two doses were not directly compared for cognitive effects in this study.

As indicated above, modafinil effects on cognition have also been studied in ADHD. In a study of 20 adult ADHD patients, a single dose of modafinil 200 mg was associated with significant enhancements in performance on digit span, visual recognition memory, spatial planning, and SSRT, relative to placebo (Turner *et al*, 2004a). The patients as a group showed slowed latencies together with increased accuracy on several measures, including the Delayed Match-to-Sample, Tower of London, and visual recognition memory tasks, suggesting that modafinil effects including shifting individuals on the speed–accuracy curve to optimize performance. In contrast, a 2-week study of 22 adult ADHD patients, where the modafinil-treated group was titrated over 4–7 days to an average dose of 206.8 mg/day, and another group received amphetamine at an average dose of 21.8 mg/day, verbal (letter) fluency was improved relative to the placebo group, but no treatment effects were observed on the Stroop or Digit Span tests (Taylor and Russo, 2000). Performance on a version of the CPT (the Test of Variables of Attention, TOVA) has also been remediated in several studies of child/adolescent ADHD patients. This includes an open-label study in 11 children with ADHD, with an average dose of 195 mg/day for an average 4.6 weeks (Rugino and Copley, 2001); a follow-up study of 22 children with ADHD, using a randomized, placebo-controlled design with an average dose of 264 mg/day for an average of 6 weeks (Rugino and Samsock, 2003); and in a recent, much larger study of childhood ADHD, which included 100 completers in the modafinil-treated group and 41 completers in the placebo group, an average dose of 361 mg for an average of 31.5 days (Greenhill *et al*, 2006). In these two latter studies, overall TOVA performance improved in the modafinil-treated

group, whereas it declined from pre-treatment baseline in the placebo group.

Summary of Effects of Modafinil on Cognition

These studies show consistent evidence for the benefits of modafinil for cognitive function. Studies in rodents indicate that modafinil can improve working memory performance in a dose- and delay-dependent manner, that the processing of contextual cues is also enhanced with modafinil, and that these effects may be augmented with sustained dosing regimens. In healthy humans (with or without undergoing sleep deprivation), working memory, recognition memory, sustained attention, and other tasks dependent on cognitive control are enhanced with modafinil. Some evidence suggests that the magnitude of modafinil effects in healthy adults may depend on underlying cognitive abilities. Among psychiatric populations, there is now consistent evidence that modafinil (in well-tolerated dosing regimens) improves attention and response inhibition in children and adolescents with ADHD; this benefit may be related to modafinil effects in modulating performance along the speed-accuracy curve for responsive individuals. Among adult psychiatric patients, there is evidence that modafinil improves several prefrontal-dependent cognitive functions in schizophrenia, major depression, and adult ADHD. Some null findings have been reported in schizophrenia; however, these studies have significant limitations evident in their design. The range of clinical samples and cognitive functions that are subject to modafinil treatment study is expected to expand in the future.

Mechanisms of Catecholamine Action in the Modulation of Cognition

The most highly elaborated model of catecholamine modulation of higher cognition has been developed for PFC dopamine in working memory, based primarily on studies of nonhuman primates. In particular, the D1 receptor in the DLPFC is critical to spatial working memory performance in monkeys (Sawaguchi and Goldman-Rakic, 1991, 1994). D1 receptors in the PFC are primarily found on the distal dendritic spines of pyramidal cells, often in conjunction with asymmetric, presumably glutamatergic synapses, and occasionally in triads which also include DA terminals (Smiley and Goldman-Rakic, 1993; Smiley *et al*, 1994; Williams and Goldman-Rakic, 1993). This may represent a post-synaptic site where D1 receptors can gate glutamatergic transmission, as D1 activation not only directly excites pyramidal neurons, but enhances the responsiveness of the post-synaptic NMDA receptor on those cells as well (Seamans and Yang, 2004). The facilitation of NMDA effects on intracellular calcium via calcyon–G_q interactions has been proposed as one of the most important functions of DA in the PFC, by not only by supporting persistent (delay-related) activity, but also by influencing both short and long-term plasticity, gene expression, and neuroadaptation (see discussion in Williams and Castner, 2006). A second major site in the PFC for the D1 receptor is at the glutamatergic terminals between neighboring pyramidal cells (Gao *et al*, 2001). At this site, D1 receptor activation leads to the attenuation of recurrent excitation within cortical microcircuitry, probably by presynaptic inhibition of glutamate release (Seamans and Yang, 2004). This may have the effect of constraining the extent of local activation during cognitive processes. A third major site of D1 receptors in PFC is on subtypes of GABAergic neurons (Muly *et al*, 1998; Sesack *et al*, 1998). This may serve to facilitate a feedforward inhibition that further restricts the extent of local circuit activity. Taken together, these three mechanisms of D1 receptor-mediated action in the PFC appear to potentiate intense focal activity, whereas dampening the responsiveness of the local surrounding circuitry that would otherwise compete with the presently active circuit (Goldman-Rakic *et al*, 2004). The information processing consequences of these physiological effects may be as follows: in a scenario of increased afferent glutamatergic activity, which informs the PFC of both when to initiate persistent activity and what the information content is, D1 receptor activation then adjusts the gain (ie, the strength of the representation) of the glutamate-encoded information in the PFC (Seamans and Yang, 2004). This includes a depression of background PFC activity, which serves to make the self-sustained activity robust to noise (eg, distractors) (Durstewitz and Seamans, 2002). A recently refined model of DA effects on PFC-mediated context processing, derived primarily from connectionist computational modeling studies, similarly suggests that optimal phasic DA action in PFC is required for the adequate processing of task-relevant stimuli, that is, the representation of contextual information (Braver *et al*, 1999), and DA serves a gating function by regulating the access of context representations into 'active' (eg, working) memory.

NE is implicated as well in PFC-dependent cognitive functions. For instance, α_2 receptors strongly modulate working memory performance in monkeys and rodents. Importantly, there does not appear to be an inverted-U-shaped curve relating working memory performance to α_2 agonist dose (Arnsten, 2004), and these effects probably occur at post-synaptic sites (Arnsten and Goldman-Rakic, 1985; Cai *et al*, 1993), where α_2 receptors are found on asymmetric (probably excitatory) synapses on dendritic spines in the PFC of monkeys (Aoki *et al*, 1994, 1998). In contrast, preferential activation of the presynaptic α_2 autoreceptor impairs working memory, probably by reducing the terminal release of NA with reduced post-synaptic α_2 receptor activation as a result (Arnsten and Goldman-Rakic, 1985). The role of post-synaptic α_2 receptor-mediated transient increases in PFC delay-related activity (Li *et al*, 1999; Sawaguchi, 1998), and associated mitigation of interference in task performance (Arnsten and Contant, 1992), suggest a point of convergence of the Arnsten model of adrenergic function with the Aston-Jones and Cohen (Aston-Jones and Cohen, 2005) model of phasic LC activity in optimizing task performance (see below).

In the Aston-Jones and Cohen (Aston-Jones and Cohen, 2005) model, phasic LC activity is driven by the outcome of task-related decision processes (signaled by descending projections from the ACC and orbitofrontal cortex), and subsequently adjusts the gain in target neurons via ascending projections back to PFC. During high (accurate) performance of visual target-detection tasks, monkeys exhibit LC activity characterized by moderate tonic activity and additional phasic responses that are selectively

observed to targets (but not distractors) (Aston-Jones *et al*, 1994). The phasic activity is not related to the sensory features or a specific reward associated with the target stimuli, and is observed even if targets are presented on every trial. In contrast, no phasic response to distractors is seen even if distractors are infrequent. Moreover, in reversal tasks, LC activity quickly re-sets to the new target and is extinguished to the new distractor; this precedes behavioral reversal within a single testing session (Aston-Jones *et al*, 1997).

Tonic LC activity, on the other hand, is proposed to facilitate disengagement of the animal from the task, because during elevations in tonic LC activity, the animal exhibits less frequent foveation to targets, lower signal-detection performance (ie, lower d and β) (Aston-Jones *et al*, 1994), and more aborted trials (Aston-Jones *et al*, 1996, 1998). This is considered adaptive in allowing the animal to pursue alternative behaviors or cognitive processes (Aston-Jones and Cohen, 2005). An important role for α_2 receptors in this model provides a link to the model described by Aston-Jones *et al* (1994). Administration of the α_2 agonist clonidine leads to decreased tonic LC activity (mediated via LC cell-body autoreceptors), with concomitant increased phasic LC activity to targets, and improved performance by decreased false-alarm and omission errors (Aston-Jones and Cohen, 2005). This reciprocal relationship between tonic and phasic modes of LC activity may be mediated by changes in the degree of electrotonic coupling between LC cells (Aston-Jones and Cohen, 2005; Usher *et al*, 1999). It appears also that when levels of tonic LC activity are minimal, such as during sleep, grooming, and eating, that phasic responses are also less robust (Aston-Jones and Bloom, 1981). This suggests that, as with other catecholamine-mediated phenomena, phasic LC activity may be related to tonic activity in an inverted-U-shaped manner. For individuals with excessively-low tonic LC activity, enhancements of both tonic and phasic LC activity may possibly be elicited in concert.

One important implication of the inverse relationship between phasic activity and moderate to high levels of tonic activity is that agents with α_2 agonist activity could act at two distinct sites to improve cognitive performance: (1) at the cell-body autoreceptor to adjust the balance of phasic to tonic LC activity in a manner to optimize decision-making performance; (2) at the post-synaptic α_2 receptor to enhance sustained PFC activity (Arnsten, 2004).

CLINICAL EFFECTS OF MODAFINIL

Modafinil has consistently shown efficacy in measures of alertness in narcolepsy and shift-work sleep disorder. Two randomized, double-blind placebo-controlled studies (with a total of 554 patients) conducted by the US Modfinil in Narcolepsy Multicenter Study Group (1998, 2000) found significant efficacy of modafinil for subjective and objective measures of wakefulness among patients with narcolepsy. Similar results have been found in smaller double-blind, placebo-controlled studies (Billiard *et al*, 1994; Broughton *et al*, 1997). In these studies and others, open-label extensions have found modafinil to have long-term efficacy for sleepiness extending for as long as 136 weeks, and to be well-tolerated, with no evidence of significant adverse events or abuse (Besset *et al*, 1996; Hirshkowitz *et al*, 2006; Mitler *et al*, 2000). Modafinil has also shown efficacy for shift work sleep disorder, with a large randomized, double-blind placebo-controlled study showing improvements in sleep latency, vigilance, sleep-related function, and the rate of automobile accidents during the post-work commute (Czeisler *et al*, 2005). Modafinil has also been evaluated for the treatment of fatigue and sedation in a number of other neurological and medical conditions, including multiple sclerosis, idiopathic Parkinson's disease, chronic fatigue syndrome, polio, HIV infection, dementias, obstructive sleep apnea, post-anaesthetic sedation, and fibromyalgia, with generally favorable but somewhat mixed results (see comprehensive summary of these studies in Ballon and Feifel, 2006). Remarkably, despite the importance of cognitive dysfunction in a range of neurological and medical illnesses, to our knowledge there have been no reports to date of modafinil effects on cognition in these disorders.

Among studies of adult psychiatric patients using clinical outcome measures, adjunct modafinil has shown efficacy in a 4-week open-label study of 11 stable patients with chronic schizophrenia or schizoaffective disorder, with dosing at 100 or 200 mg/day (Rosenthal and Bryant, 2004). Of the patients, 82% completed the study, and a blinded clinician rated 64% of patients as clinically improved at week 4, using CGI and the Global Assessment of Function, with fatigue scores also improved. PANSS scores were unchanged, indicating that positive symptoms were not exacerbated, and no serious adverse events were detected. A randomized, placebo-controlled 8-week study of adjunct modafinil 100 or 200 mg/day in 13 schizophrenia patients (and 11 patients receiving placebo) found no changes in positive or negative symptoms (Sevy *et al*, 2005). Two studies of patients with major depression have been reported. In the first, a 4-week open-label adjunct modafinil (with flexible dosing from 100–400 mg/day) was associated with significant improvements in the Beck Depression Inventory, Hamilton Depression Rating Scale (Ham-D) and CGI, as well as measures of fatigue (DeBattista *et al*, 2004). The other study was a multicenter, randomized, placebo-controlled 8-week study of adjunct modafinil 200 mg/day (added to concurrent treatment with selective serotonin reuptake inhibitors), which found an 85% completion rate (of 311 patients who received at least one dose), and significant improvements in Ham-D, MADRS, and sleepiness ratings compared to placebo (Fava *et al*, 2005). Adverse events significantly associated with modafinil included nausea (9 *vs* 2% on placebo) and feeling jittery (4 *vs* 1%). In a 12-week, open-label extension study of these depressed patients, with modafinil doses titrated following the initial 8-week placebo-controlled study cited above, the initial modafinil non-responders showed a significantly greater clinical response on all measures than the initial treatment-responsive group (Thase *et al*, 2006). In an 8-week randomized, double-blind placebo-controlled study of 62 cocaine-dependent adults, modafinil 400 mg/day was associated with greater rates of urine samples that were negative for a cocaine metabolite, and of achievement of at least 3 weeks of complete abstinence from cocaine use (Dackis *et al*, 2005). Of the patients, 65% completed the study, and

no serious adverse events were noted. A randomized, double-blind, placebo-controlled three-phase crossover study of 22 adults with ADHD found improvements in DSM-IV ADHD Behavior Checklist for Adults compare to placebo, for both modafinil (2 weeks after titration to mean 207 mg/day) and amphetamine (Taylor and Russo, 2000).

Among child and adolescent psychiatric disorders, modafinil has only been studied to date in ADHD. It has been found to improve parent, teacher, and clinician ratings of ADHD symptoms in open-label treatment of 11 medication-free children with an average dose and duration of 195 mg/day (range 100–400 mg) and 4.6 weeks (range 2–7 weeks) (Rugino and Copley, 2001). In a follow-up study of 22 children with ADHD, this time employing a randomized, placebo-controlled design with an average dose of 264 mg/day (range 200–300 mg) for an average of 6 weeks, they found the modafinil-treated group to exhibit significantly greater improvement than the placebo group on the Conners Rating Scales ADHD total score (Rugino and Samsock, 2003). The Modafinil ADHD Study Group has conducted several randomized, double-blind placebo-controlled studies of modafinil in children and adolescents with ADHD. In a 4-week study with 223 children (aged 6–13 years) completing the study, the group receiving 300 mg/day showed a significantly greater improvement in the teacher-rated ADHD Rating Scale-IV (ADHD-RS-IV), clinician-rated ADHD-RS-IV, and the parent-rated Conners ADHD/DSM-IV scales (Biederman *et al*, 2006). In a 7-week study with 190 ADHD patients (aged 6–17 years) enrolled, the modafinil-treated groups (receiving either 340 mg ($n=44$) or 425 mg ($n=82$), based on body weight) showed significantly greater improvement on the ADHD-RS-IV School and Home versions and on the CGI (Swanson *et al*, 2006). In a 9-week multicenter study of children and adolescents with ADHD (aged 7–17 years) that included 100 completers in the modafinil-treated group and 41 completers in the placebo group, modafinil at an average dose of 361 mg (range 170–425 mg) for an average of 31.5 days (range, 2–56 days) was associated with a significantly greater improvement in the ADHD-RS-IV School and Home versions, and on the Clinical Global Impression (CGI) scale (Greenhill *et al*, 2006). And in a 9-week multicenter study of children and adolescents with ADHD, the modafinil-treated group ($n=164$), receiving an average dose of 368.5 mg/day (range 170–425 mg) showed greater improvements in the ADHD-RS-IV School and Home versions, and on the CGI, compared to the placebo-treated group (Biederman *et al*, 2005). The significant group differences in ADHD-RS-IV School version were apparent in the first week of treatment and maintained throughout the treatment period.

Throughout these clinical intervention studies, modafinil has been well tolerated. Nevertheless, case reports have appeared describing significant adverse events in routine clinical use of modafinil. One case report has appeared describing exacerbation of psychosis in a 61-year-old inpatient, with schizophrenia and hypertension, after initiation of modafinil treatment (Narendran *et al*, 2002). This patient received a 3-week regimen of 800 mg/day added to existing treatment with clozapine 300 mg/day, lorazepam 1 mg/day, and amlodipine 40 mg/day. The patient is reported to have stabilized within 2 weeks after discontinuation of modafinil (including severity of positive psychotic symptoms) with no other medication changes, and there is no indication in the report of serious sequelae in the intervening period of worsened psychosis. Whereas other single case reports have appeared describing adverse events in the treatment of psychiatric patients such as clozapine toxicity (Dequardo, 2002), premature ventricular contractions (Oskooilar, 2005), induced mania (Vorspan *et al*, 2005; Wolf *et al*, 2006), and irritability and verbal aggression (Ranjan and Chandra, 2005), these events have not been observed at a significant rate in modafinil-treated patients compared to placebo-treated patients in the clinical trials cited above. Modafinil also appears to have a relatively low potential for abuse, which may be a function of its pharmacodynamic profile and/or its physical properties, being insoluble in water and unstable at high temperatures, which minimizes its bioavailability upon smoking or intravenous use (Jasinski, 2000; Myrick *et al*, 2004). In addition, a preliminary study of 12 cocaine-dependent adults suggests that modafinil (up to 800 mg as an open-label single-dose) does not exhibit interacting effects with 40 mg intravenous cocaine on hemodynamic measures (Malcolm *et al*, 2006).

Modafinil effects on anxiety have also been measured, in animal models and in humans. One study found that whereas amphetamine increased three measures of anxiety in mice, with increased latency of exploration of a white compartment, increased open-field thigmotaxis, and decreased time in the open arms of an elevated-plus maze, modafinil lacked these effects at doses that induce comparable effects on locomotor activity (Simon *et al*, 1994). A study of wake-promoting effects in monkeys reported no significant observations of anxiety responses to modafinil after single or repeated doses that increased nocturnal activity (Hermant *et al*, 1991). In contrast, a pharmacokinetic study of modafinil (at doses from 200–800 mg p.o. over 7 days) in healthy subjects found 21% to indicentally report subjective anxiety (although rates of self-reported anxiety among the placebo group are not reported) (Wong *et al*, 1999b). A study of mood and cognitive function in healthy young adults found a single 100 mg dose of modafinil to be associated with increased subjective and physical symptoms of anxiety (eg, restlessness, muscular tension, shaking) than placebo, although the higher dose (200 mg) did not show these effects (Randall *et al*, 2003). A study of healthy adults given modafinil 400 mg p.o. daily for 3 days found relatively decreased self-reported scores compared to placebo on the Calm scale of the Positive- and Negative-Affect Scale (Taneja *et al*, 2007). Interestingly, in this study, both overall positive and negative affect was relatively increased on modafinil. Among myotonic dystrophy patients, modafinil (100 mg p.o. daily for 14 days) increased self-reported scores on the tension–anxiety index of the Profile of Mood States (along with increased vigor-activity and decreased fatigue-inertia) compared to placebo (MacDonald *et al*, 2002). Two studies of obstructive sleep apnea patients reported on anxiety. In one, rates of anxiety were 6% on modafinil *vs* 1% on placebo (during the double-blind phase) and 16% after 12 weeks of open-label modafinil (200–400 mg/day) (Schwartz *et al*, 2003). In the second, rates of anxiety were 5.3% on armodafinil (150 and 250 mg/day) *vs* 2% on placebo (Roth *et al*, 2006). A study of 50 multiple sclerosis patients found three leading to

drop out or dose reduction due to nervousness or restlessness (Zifko *et al*, 2002). It does appear, therefore, that modafinil (at clinically-effecive doses) is associated with increased anxiety in healthy individuals and clinical populations, although it is unclear if this is dose-related.

CONCLUSION

Modafinil is an agent with a rapidly expanding list of off-label uses in neurology, medicine, and psychiatry. It appears to have multiple effects on catecholamine systems in the brain, including DAT and NET inhibition, and elevation of extracellular catecholamines, glutamate, serotonin, and HA, activation of the orexinergic system, and decreased GABA. Alpha-adrenergic, D1 and D2 receptors in the brain mediate modafinil effects on waking and activity, and may also mediate the neurochemical effects on these other neurotransmitter systems. Modafinil is also significantly different from amphetamine in structure and profile of neurochemical and behavioral effects. Intriguing preliminary evidence suggests that modafinil may be relatively selective for cortical over subcortical effects. In the clinical setting, modafinil shows efficacy in a number of neurological and psychiatric illnesses, with a significantly improved side-effect profile compared to amphetamine, including a relatively low liability to abuse. Equally important, there is now increasing evidence that modafinil can improve cognitive function, particularly working memory, episodic memory, and processes requiring cognitive control. Studies in animal models and neuroimaging in humans suggest that these effects may be related to specific actions of modafinil in the frontal cortex. The remediation of cognitive dysfunction and related neural activity may in turn form the basis of the clinical efficacy of this agent, across a range of neuropsychiatric disorders. Further investigation is necessary to confirm these initial findings, to identify specificity of these effects in the domains of neurochemistry, neuroanatomy, and cognition, and to evaluate other factors relevant to clinical use, such as the relationship of single-dose to sustained dosing regimens, and the relationship of pro-cognitive effects to clinical outcome.

DISCLOSURE/CONFLICTS OF INTEREST

Dr Minzenberg and Dr Carter have received research funding from Cephalon, a manufacturer of modafinil and armodafinil. Dr Carter has served as a consultant for Pfizer, Hoffman La Roche, and Lilly. Dr Minzenberg holds stock in Elan Pharmaceuticals. No support was received from these companies in the background research for, or preparation of, the present manuscript. Funding to support this work was received from a Translational Clinical Scientist Award from the Burroughs Wellcome Foundation, and MH59883 and MH066629 from the NIMH, all to Dr Carter.

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