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Approaches to Measuring the Effects of Wake-Promoting Drugs: A Focus on Cognitive Function

Christopher J. Edgar¹, Edward F. Pace-Schott², and Keith A. Wesnes³

¹ Consultant Psychologist, Reading UK

² Department of Psychiatry, Center for Sleep and Cognition, Harvard Medical School, Beth Israel-Deaconess Medical Center, Boston, Massachusetts, USA

³ Cognitive Drug Research Ltd, UK

Abstract

Objectives—In clinical drug development, wakefulness and wake-promotion may be assessed by a large number of scales and questionnaires. Objective assessment of wakefulness is most commonly made using sleep latency/maintenance of wakefulness tests, polysomnography and/or behavioral measures. The purpose of the present review is to highlight the degree of overlap in the assessment of wakefulness and cognition, with consideration of assessment techniques and the underlying neurobiology of both concepts.

Design—Reviews of four key areas were conducted: commonly used techniques in the assessment of wakefulness; neurobiology of sleep/wake and cognition; targets of wake promoting and/or cognition enhancing drugs; and ongoing clinical trials investigating wake promoting effects.

Results—There is clear overlap between the assessment of wakefulness and cognition. There are common techniques which may be used to assess both concepts; aspects of the neurobiology of both concepts may be closely related; and wake promoting drugs may have nootropic properties (and vice-versa). Clinical trials of wake promoting drugs often, though not routinely, assess aspects of cognition.

Conclusions—Routine and broad assessment of cognition in the development of wake promoting drugs may reveal important nootropic effects, which are not secondary to alertness/wakefulness, whilst existing cognitive enhancers may have under explored or unknown wake promoting properties.

Keywords

wake-promoting; sleep-wake cycle; cognition; drug development

Objectives

Excessive sleepiness or excessive daytime sleepiness may be reported by large numbers of adults. Half of all respondents in the 2005 American National Sleep survey reported that they felt tired, fatigued or 'not up to par' on at least one day a week, and 17% said this happened every day, or almost every day (2005). Syndromes associated with excessive daytime sleepiness (EDS) include: insufficient or fragmented sleep; sleep related breathing

disorders (e.g. obstructive sleep apnoea/hypopnea syndrome (OSAHS)); narcolepsy; idiopathic hypersomnia; Kleine-Levin syndrome; circadian disorders (e.g. shift-work sleep disorder (SWSD)); nervous system disorders (e.g. stroke, multiple sclerosis, Alzheimer's disease and Parkinson's disease); psychiatric disorders (e.g. depression); and drug effects themselves (e.g. sedative hypnotics, antihistamines and antidepressants) as well as effects of abused substances (Guilleminault and Brooks, 2001). Effective pharmacotherapy for EDS is available and the most commonly used drugs include dextroamphetamine, methylphenidate, modafinil, armodafinil (Guilleminault and Brooks, 2001). Caffeine and nicotine are also widely used for their psychostimulant properties in the general population. Also wake-promoting are drugs that secondarily enhance wakefulness by improving nocturnal sleep quality (e.g., GHB, hypnotics and sedating antidepressants). Cognitive impairment is well recognized in EDS disorders. Similarly, disorders in which cognitive impairment is recognized as a primary symptom such as dementia, schizophrenia and attention deficit disorder (ADHD), may also be associated with EDS and sleep disruption. Nonetheless, it should also be recognized that EDS and cognitive dysfunction may not always co-occur (Kloss et al., 2002, Nofzinger and Keshavan, 2002). There are a large number of approaches to measuring wakefulness and thus the effects of wake-promoting drugs (Table I). These different approaches have advantages dependent on a number of factors including: the phase of clinical development; the subject/patient population studied; trial design considerations; and the mechanism of action of the drug itself. In addition to this, appropriate test validation and the relative psychometric and/or statistical properties of each assessment and their independence and inter-relationships in measuring different aspects of wakefulness are also important considerations.

The purpose of the present review will be to consider the range of assessment approaches used in the study of wake-promoting drugs, including registered pharmacotherapy, recreational drugs, and those in clinical development. The application of these different assessment approaches will be discussed, with reference to specific wake promoting drugs and the underlying neurobiology of the sleep-wake cycle. In particular, cognition assessment will be discussed as a measure of wakefulness, and the broader implications of the overlap between wakefulness and cognition considered.

Relationships between the neurobiology of the sleep-wake cycle and the neurobiology of cognition

Studies of the neurobiology of the sleep-wake cycle (behavioral state) implicate neurotransmitters and neurotransmitter systems broadly overlapping with those implicated in the regulation of cognitive functions including Acetylcholine (ACh); Gamma-aminobutyric acid (GABA); Dopamine (DA); Histamine (HA); Orexin (hypocretin); Melatonin; Norepinephrine (NE); Serotonin (5-HT) and adenosine (AD). It may be possible, therefore, to predict cognitive effects of certain drugs that influence these systems based upon their effect on behavioral state. Drugs affect behavioral state via diverse neural processes that may produce correspondingly variable effects on cognition. Processes thus influenced are discussed below and include: (i) the general state of cortical arousal mediated by the ascending reticular activating system (ARAS) and its neuromodulators and opposed endogenously by inhibitory GABA mechanisms and exogenously by GABAergic drugs; (ii) central mechanisms underlying sleep onset (e.g., the hypothalamic sleep switch, sleep stabilization, sleep offset/inertia and stabilization of waking); (iii) the sleep homeostat and circadian oscillator that regulate sleep propensity via interactive processes described in Borbely's 2-Process Model; and (iv) cognitive processes, such as memory consolidation, that are themselves dependent upon sleep.

Cortical arousal

In waking, the positive association of cortical arousal with performance across multiple cognitive domains is well documented albeit mediated by the Yerkes-Dodson Law whereby moderate levels of arousal produce better performance than low or high extremes e.g., (Anderson, 1994, Watters et al., 1997). Although the current review focuses on cortical arousal and cognitive effects of wake-promoting versus somnogenic agents, it must be remembered that rapid eye movement (REM) sleep is also a state of cortical arousal that is accompanied by what can be considered impaired cognitive function relative to waking (Hobson et al., 2000). In waking, multiple neurochemical systems with overlapping functions maintain cortical arousal (Saper et al., 2005b). These include: (i) ACh from the basal forebrain (BF) and pedunculopontine and laterodorsal tegmental nuclei of the mesopontine brainstem (PPT/LDT); (ii) NE from the locus coeruleus (LC); (iii) 5-HT from the dorsal raphe (DR); (iv) DA from specifically wake-active centers in the periaqueductal gray (PAG) see (Lu et al., 2006) as well as from substantia nigra pars compacta (SNpc) and ventral tegmental (VTA) areas of the midbrain (subserving movement and appetitive behaviors respectively); (v) HA from the tuberomammillary nucleus (TMN) of the posterior hypothalamus; and (vi) orexin from the lateral and posterior hypothalamus (Sakurai, 2007, Saper et al., 2005b).

With the transition from waking to non-REM (NREM) sleep, neuronal firing rates in all these wake-active nuclei decline below waking levels and continuing to decline with deepening NREM. In the transition from non-REM (NREM) to REM sleep, firing of LC, DR and TMN neurons and respective levels of NE, 5-HT and HA at their terminal fields decline further to their minimum levels. In contrast, firing rates of PPT/LDT neurons return to levels comparable to waking (Pace-Schott and Hobson, 2002b, Saper et al., 2005b). In a third pattern, DA (Lena et al., 2005) and orexin (Kiyashchenko et al., 2002, Sakurai, 2007), neurochemical release at certain terminal fields is phasically higher in both waking and REM than in NREM. Despite unchanged mean firing rates of SNpc and VTA neurons across behavioral state (Monti and Monti, 2007), synaptic levels of DA increase in REM when VTA neurons shift from tonic to burst firing modes (Dahan et al., 2007, Monti and Jantos, 2008). Cholinergic activation of the thalamus and BF by the PPT/LDT desynchronizes (activates) the cortex in REM by disrupting intrinsic thalamocortical rhythms of NREM (Steriade, 2004, Steriade, 2000) and promoting cholinergic activation of the cortex by the BF (Jones, 2005, Sarter and Bruno, 2000). Cognitive activity during REM consists of dreams in which markedly deficient memory, attention and executive function can be attributed to cortical activation primarily by ACh in the absence of monoaminergic (NE, 5-HT, HA) modulation (Pace-Schott et al., 2005).

Pharmacological agents influencing behavioral state in predictable ways via each of these systems have corresponding effects on cognitive domains dependent upon alert waking such as attention (NE), working memory (DA, NE), memory encoding (NE, ACh) and executive functions (NE, DA, 5-HT). In most general terms, agents potentiating waking facilitate and those potentiating sleep disfacilitate these functions again, however, with caveats necessitated by the Yerkes-Dodson law and diverse effects at receptor targets (e.g., pre-synaptic or somatodendritic autoreceptors versus post-synaptic heteroreceptors).

For example, at the facilitatory pole, cholinergic augmentation via nicotinic (nicotine from tobacco) or muscarinic (arecholine from betel) receptors both enhances alertness (Chu, 2002, Rezvani and Levin, 2001) and lightens sleep (Davila et al., 1994, Joseph and Sitaram, 1990). Cholinergic mechanisms improve signal to noise processing in the cortex (Everitt and Robbins, 1997), processes critical to memory and attention that are disrupted in the hypocholinergic states of Alzheimer's disease, Lewy body dementia and antimuscarinic delirium (Perry and Perry, 2004). Functional neuroimaging studies in humans of cholinergic

enhancement with acetylcholinesterase inhibitors or agonists as well as blockade by muscarinic antagonists have begun to reveal the brain bases of cognitive enhancement by ACh (reviewed in Thiel 2003 (Thiel, 2003)). Nicotinic stimulation may bias attentional mechanisms toward external over endogenous stimuli (daydreaming, rumination, etc.) by deactivating the brain's default network (Hahn et al., 2007) – a group of midline cortical and hippocampal structures that activate when attention is unoccupied by external foci and that is believed to support adaptive, self-relevant cognition (Buckner et al., 2008).

Similarly, cognitive performance can be enhanced by substances that promote waking via enhanced monoaminergic neurotransmission. Dopaminergic psychostimulants such as amphetamine and methylphenidate elevate synaptic DA via reuptake blockade and reverse transport producing potent wake-promoting and sleep-disruptive behavioral effects. Consequently, before the advent of newer agents such as modafinil, amphetamine-like psychostimulants were the treatment of choice for disorders of excessive daytime sleepiness such as narcolepsy (Mignot and Nishino, 2005). Notably, however dopaminergic effects on sleep-waking are highly dependent on receptor target with D1 stimulation producing arousal, D2 stimulation producing sedation at low doses (due to autoreceptor activation) but arousal at high doses (due to postsynaptic actions) and D3 stimulation favoring sleep (Monti and Monti, 2007). Similarly, DA agonists such as bromocriptine and pramipexole, given for Parkinson's disease, can produce sedation and sleep attacks (Etminan et al., 2001) due again to autoreceptor stimulation (Monti and Monti, 2007).

Potential of serotonergic neurotransmission with selective serotonin reuptake inhibitors lightens NREM sleep and disrupts sleep continuity (Oberndorfer et al., 2000) whereas antagonism of 5-HT₂ receptors with ritanserin or ketanserin promotes slow wave sleep or SWS (Sharpley et al., 1994). Newer 5-HT₂ receptor antagonists are in development for sleep disorders (e.g. Sanofi-Aventis compounds eplivanserin and volinanserin; Eli-Lilly compound pruvanserin). Whereas potentiation of noradrenergic neurotransmission with selective norepinephrine reuptake inhibitors can promote wakefulness and produce mild sleep disturbance (Bart Sangal et al., 2008, Kuenzel et al., 2004) and the noradrenergic agonist ephedrine powerfully promotes waking (Gyllenhaal et al., 2000), as in the case of DA, activation of presynaptic NE autoreceptors with low doses of alpha₂ agonists (e.g., clonidine) can be somnogenic (Miyazaki et al., 2004). Sleep effects of histaminergic agents have been largely defined by their antagonists, the antihistamines, older varieties of which cross the blood-brain barrier producing sedation by action at central H₁ receptors (Adelsberg, 1997, Barbier and Bradbury, 2007). Lastly, modafinil potentiates a number of arousal systems, especially catecholaminergic mechanisms, and has a powerful wake-promoting action (Minzenberg and Carter, 2007).

With regard to cognitive enhancement by monoamines, working memory is improved by dopaminergic psychostimulants such as methylphenidate (Chamberlain et al., 2006), DA agonists such as bromocriptine (Mehta and Riedel, 2006) or activation of prefrontal postsynaptic alpha₂ noradrenergic receptors by clonidine or guanfacine (Ramos and Arnsten, 2007).

However, as in the case of sleep-waking effects, an important caveat is that aminergic agents produce cognitive enhancement at some dosages, receptors or anatomic targets or on certain cognitive tasks but with no effect or even impaired performance on others (Ramos and Arnsten, 2007, Mehta and Riedel, 2006). For example, dopaminergic effects on attention and executive function follow the Yerkes-Dodson relationship with enhancement at moderate but impairment at high levels (Robbins, 2005, Chamberlain et al., 2006).

Similarly, low to moderate levels of NE enhance attention and working memory by action on more sensitive prefrontal α_2 adrenergic receptors whereas high levels impair these same functions by acting on α_1 and beta receptors (Ramos and Arnsten, 2007). This latter effect occurs because mode of discharge (phasic versus tonic) rather than mean firing level is the critical factor determining attentional performance (Aston-Jones and Cohen, 2005).

Enhancement by serotonergic agents may be highly specific for certain cognitive functions while impairing others (Chamberlain et al., 2006, Cools et al., 2008, Schmitt et al., 2006). Serotonergic pathways are known to be critical to learning and memory (Meneses, 1999) and, possibly through inhibitory actions on ACh, DA and NA, are also implicated in attentional processes (Wingen et al., 2007). Consequently, serotonergic receptor sub-types are also a target for drugs aimed at improving cognition for example 5-HT_{1A} agonism (Wyeth, Sanofi-Aventis), 5-HT₆ antagonism (Memory, Roche, and GSK) and 5-HT₄ agonism (EPIX).

Whereas central antagonism of HA by old generation antihistamines was accompanied by cognitive impairment (Adelsberg, 1997), newer, non-sedating antihistamines may actually improve attentional function via effects on dopaminergic or GABAergic systems (Theunissen et al., 2006). Lastly, combined potentiation of diverse monoaminergic systems by modafinil has shown positive effects on many of the attentional, executive and mnemonic functions enhanced by more neurochemically specific monoaminergic treatments (Minzenberg and Carter, 2007).

A key brain region modulated by wake-promoting neuromodulators including ACh (Thiel, 2003), NE (Ramos and Arnsten, 2007), DA (Robbins, 2005) and 5-HT (Cools et al., 2008) is the prefrontal cortex, different sub-regions of which may be preferentially influenced by different neuromodulators. Notably, relative prefrontal quiescence seen with EEG is one of the first physiological signs of sleep. Such signs include increased spectral power in the slower frequencies characteristic of SWS (slow wave activity or SWA) seen in the electroencephalogram (EEG) or magnetoencephalogram (MEG) and decreased regional cerebral blood flow seen using functional neuroimaging – for reviews see (Pace-Schott, 2007, Muzur et al., 2002).

On the disfacilitatory pole, GABAergic neurotransmission plays a key role in the initiation and maintenance of sleep (see below). The benzodiazepines potentiate GABAergic activity, have powerful sedative/hypnotic effects (Dundar et al., 2004) and can produce marked cognitive impairment (Buffett-Jerrott and Stewart, 2002, Barker et al., 2004). However, due to the “excitatory” results of inhibiting centrally ubiquitous GABAergic interneurons (i.e., disinhibition of their targets), there is considerable regional diversity in the effects of GABA on both behavioral state and cognition. For example, enhanced GABAergic neurotransmission in the oral pontine reticular formation, a sleep-promoting region of the brainstem, enhances wakefulness (Xi et al., 1999) and both GABA levels and waking are increased when orexin is dialyzed into this region (Watson et al., 2008). Similarly, GABAergic mechanisms for control of the other forebrain-activated state, REM sleep, involving mutually inhibitory circuits among GABAergic brainstem nuclei have also been recently proposed (Lu et al., 2006, Luppi et al., 2006). Interestingly, regionally targeted (hippocampal) enhancement of GABAergic neurotransmission with a receptor subtype-specific inverse agonist is under pre-clinical investigation for potential memory enhancement (Maubach, 2003).

The sleep-wake switch

Saper and colleagues have proposed that a neural circuit centered in the hypothalamus controls sleep-wake transitions (Saper et al., 2001, Saper et al., 2005b). Sleep-active neurons in the ventrolateral preoptic area (VLPO) of the anterior hypothalamus, producing GABA and the inhibitory neuropeptide galanin, project to and inhibit the hypothalamic (TMN), basal forebrain and brainstem (LC, DR, PPT/LDT) neurons that produce the wake-promoting monoamines (NE, 5-HT and HA) and acetylcholine. The aminergic LC, DRN and TMN neurons reciprocally project to and inhibit the VLPO thus forming a “flip-flop” circuit in which sleep and waking constitute self-reinforcing stable states that contrast with highly transient intermediate conditions (Saper et al., 2001, Saper et al., 2005b).

Once NREM sleep is established, it is stabilized by continued GABAergic inhibitory output to arousal-related nuclei from the VLPO, *cfos* activity in which correlates with duration of sleep in rats (Saper et al., 2001) and which may contain specific cell populations supporting NREM and REM sleep (Saper et al., 2005b). NREM sleep is additionally maintained by endogenous slow oscillations in thalamocortical circuits that are measured by scalp EEG as activity in the delta and slow (<1 Hz) frequencies as well as the sleep spindle and K-complex wave forms (Steriade, 2000, Steriade, 2006).

A key regulator of waking pole of this system is the excitatory neuropeptide orexin (hypocretin) that is produced by lateral and posterior hypothalamic (LH) neurons that project to, excite and maintain the sustained activity of wake-promoting neurons of the TMN, BF, LC, DR and PPT/LDT (Sakurai, 2007, Saper et al., 2001, Saper et al., 2005b). When this drive is attenuated in narcolepsy, an orexin-deficient condition, the mutually inhibitory circuit between VLPO and arousal systems produces abnormally rapid shifts from waking to sleep. Orexinergic neurons additionally project to the dopaminergic VTA, the arousal-related paraventricular thalamic nucleus, stress-response related periventricular hypothalamic and central amygdalar nuclei, as well as to the feeding-related arcuate nucleus of the hypothalamus (Sakurai, 2007). These efferents, in combination with afferents to orexin neurons from many of these same systems, suggest that orexin promotes behavioral arousal and limbic activation in the service of reward, appetitive and threat-related behaviors key to survival (Sakurai, 2007).

The offset of sleep (awakening) is often accompanied by persistence of the diminished arousal of sleep carried over into waking, a condition that has been termed “sleep inertia” (Dinges, 1990, Ferrara and De Gennaro, 2000). This condition results in impaired alertness and performance lasting several minutes to several hours and is more severe following awakening from de-aroused, deep sleep (i.e., SWS) than from the brain activated state of REM (Merica and Fortune, 2004). Within individuals, cognitive impairment due to sleep inertia can exceed that of sleep deprivation (Wertz et al., 2006). Because sleep deprivation increases homeostatic sleep pressure and SWA (see below), it can also intensify sleep inertia especially if one is awakened from SWS as may occur from a nap. Similarly, sleep inertia is greater if one is awoken at the circadian minimum drive to waking, one’s “biological night,” regardless of whether one’s circadian clock (see below) is entrained to normal daytime waking and nighttime sleep of another schedule (Scheer et al., 2008). Notably, as at sleep onset and all throughout sleep, neuroimaging studies have shown that the sleep inertia period is characterized by relative prefrontal cortical deactivation (Balkin et al., 2002). Effects of sleep inertia may be reduced or eliminated by wake-promoting agents such as caffeine (Van Dongen et al., 2001) and sleep-inertia may be a legitimate target for treatment strategies e.g. in shift-workers (Tassi and Muzet, 2000).

The sleep homeostat and circadian oscillator

Borbely's two-process model suggests that sleep-wake transitions are controlled by integrated activity of homeostatic (Process S) mechanisms, that increase sleep drive as a function of prior wake time, and circadian (Process C) mechanisms that regulate sleep propensity as a function of time-of-day under control of the suprachiasmatic nucleus (SCN) of the hypothalamus (Hofer-Tinguely et al., 2005). Homeostatic sleep pressure is indexed by EEG spectral power in the slow delta range (Slow Wave Activity or SWA) following sleep onset whereas circadian phase is best determined by plasma melatonin or core body temperature. Cognitive abilities are strongly influenced by both processes alone and in concert.

Elevating homeostatic sleep pressure via sleep deprivation degrades vigilant attention (Lim and Dinges, 2008), working memory (Turner et al., 2007) and executive function (Harrison and Horne, 2000), effects shared by sleep restriction (Banks and Dinges, 2007) and fragmentation (Bonnet and Arand, 2003), remediation of which are key targets of wake-promoting medications such as modafinil and amphetamines (Bonnet et al., 2005). Brain bases of cognitive deficits resulting from sleep loss (Chee and Chuah, 2008) as well as mechanisms by which alerting drugs counter these deficits (Thomas and Kwong, 2006) are additionally under intense study.

Homeostatic sleep pressure is believed to result from substances that accumulate in the brain in proportion to time awake (endogenous somnogens). Among candidate endogenous somnogens, most evidence currently exists for adenosine (Landolt, 2008) acting through its A1 (Basheer et al., 2004) and A2A (Huang et al., 2007) receptors in sleep-related regions of the hypothalamus, basal forebrain and ventral striatum, although there is also evidence for cytokine endogenous somnogens such as prostaglandin D2 (Huang et al., 2007). A number of mechanisms have been proposed whereby accumulating adenosine at specific brain sites such as the BF and anterior hypothalamus triggers initial stages in the switch from waking to sleep via the VLPO-arousal nuclei flip-flop circuitry (Basheer et al., 2004, Saper et al., 2005b).

Recently, a potential genetic basis for inter-individual differences in SWA has been identified in a functional polymorphism of adenosine deaminase (Landolt, 2008). As a non-specific adenosine receptor antagonist, caffeine acts directly upon this mechanism by antagonizing A1 receptors on wake-promoting BF cholinergic neurons (Basheer et al., 2004) as well as A2A receptors at other subcortical sites (Huang et al., 2007). A complementary alerting mechanism of caffeine may result from antagonism of A1 and A2A receptors that oppose the activating effect of DA on DA receptors co-expressed on striatal neurons (Ferre et al., 1997, Fisone et al., 2004).

Circadian rhythms are controlled by endogenous molecular clocks in neurons of the SCN that transmit reliable signals with 24-hour periodicity via several hypothalamic centers to all regions of the CNS (Saper et al., 2005a). Circadian factors also influence normal cognitive functioning in attention, memory and executive domains (Schmidt et al., 2007). Melatonin, produced under SCN control by the pineal gland, provides feedback control of circadian rhythms via SCN melatonin receptors that are target of hypnotic drugs such as melatonin (Pandi-Perumal et al., 2007) and ramelteon (Sateia et al., 2008). Additionally, circadian factors underlie individual performance differences based upon eveningness or morningness (chronotype) as well as developmental changes in chronotype including phase delay at adolescence (Crowley et al., 2007) and phase advance in ageing (Cooke and Ancoli-Israel, 2006). Discovery of normative phase delay at adolescence has generated educational policy discussions as to whether later start times may improve cognitive (academic) performance in high school students (Crowley et al., 2007). Melatonin-related hypnotics are especially

effective in treating circadian-phase related insomnia (Pandi-Perumal et al., 2007, Sateia et al., 2008). The cognition-enhancing role of these substances as well as the GABAergic hypnotics that improve sleep in insomnia (i.e., benzodiazepines, eszopiclone, zolpidem, zaleplon) or narcolepsy (e.g., sodium oxybate) is to enhance daytime cognitive functioning secondary to these hypnotics' improvement of nocturnal sleep. In contrast, improper timing or dosage of hypnotics can cause profound impairment of cognitive performance during subsequent waking e.g., (Storm et al., 2007). In addition, abuse liability of sedative hypnotic agents and in particular sodium oxybate (GHB) is an important concern (Carter et al., 2006).

Sleep dependent memory

Lastly, there are an ever-expanding number of studies demonstrating sleep-dependency for memory consolidation on both procedural and declarative memory tasks as well as for implicit and explicit rule extraction (reviewed in (Walker and Stickgold, 2006) and (Stickgold and Walker, 2007)). Such tasks require intervening sleep for optimal re-test performance and performance may strongly correlate with and in some cases has been causally linked with specific sleep stages (reviewed in (Walker and Stickgold, 2006) and (Stickgold and Walker, 2007)). For such tasks, performance enhancing pharmacological interventions would strive to optimize sleep quality or specific sleep stages (e.g., SWS). For example, on one such task, sleep-dependent improvement on a mirror-tracing (procedural memory) task was impaired in insomniacs compared to normals whereas in another (Backhaus et al., 2006), a paired associates (declarative memory) task was similarly impaired. Pharmacological treatment to enhance performance of such tasks in insomnia might, therefore, focus on enhancing sleep depth or continuity.

Summary

It is clear then that changes in a number of neurotransmitters and neurotransmitter systems may have implications for both the sleep-wake cycle and cognition. Importantly, these cognitive consequences are not restricted to attention/concentration, those aspects of cognition are commonly associated with wakefulness, but may also have implications for a range of other functions such as learning and memory, working memory and executive functions. A further important point is that the disorders primarily associated with EDS(narcolepsy, OSAHS, SWSD) may also be associated with cognitive dysfunction (Kloss et al., 2002), whilst conditions primarily associated with cognitive/behavioural disturbances are also associated with disrupted sleep (e.g. Alzheimer's disease, Parkinson's disease, schizophrenia and depression) (Nofzinger and Keshavan, 2002), thus serving to illustrate the large potential for concurrent changes in both wakefulness and cognition.

Wake promoting drugs

Despite increasing recognition of the prevalence of EDS and also its social and economic consequences in terms of productivity, accident risk and quality of life (2005), there are few drugs for EDS in active clinical trials. Clinicaltrials.gov lists ongoing studies of direct wake promoting effects for two compounds: armodafinil and the Merck H3 antagonist MK-2049; whilst the melatonin receptor agonist ramelteon is under investigation in several studies investigating wake promoting effects, secondary to improved sleep. Consideration of recently completed studies show that Alza (JNJ-17216498) and GSK (GSK189254) have histamine H3 antagonists in development for narcolepsy; and the Vanda drug VSF-173, of unknown mechanism of action, is in development for excessive sleepiness. Other mechanisms (e.g., hypocretin/orexin neurotransmission) are at earlier stages of investigation. Armodafinil is also being evaluated specifically in schizophrenia for effects on cognition, as well as specific cognitive deficits associated with OSA/HS, whilst MK0249 is being

evaluated to treat cognitive impairment associated with schizophrenia, Alzheimer's Disease (AD) and attention deficit hyperactivity disorder (ADHD) (Table II).

Amphetamine-like stimulants

Amphetamine-like stimulants include dexamphetamine, methamphetamine, pemoline, cocaine, bupropion, ephedrine/pseudoephedrine and methylphenidate. Amphetamines broadly act as both dopaminergic and noradrenergic reuptake inhibitors to varying degrees. Several other mechanisms of action including: amphetamine-induced exchange diffusion, reverse transport, channel-like transport phenomena and the weak base properties of amphetamine are important. Additional effects on monoamine transporters through phosphorylation, transporter trafficking, and the production of reactive oxygen and nitrogen species may also be relevant (Fleckenstein et al., 2007). They are potent stimulants and used in the treatment of EDS (Schwartz, 2004), as well as attentional disorders (Cohen et al., 2006).

Self-reported Effects

Prototypical subjective effects of amphetamine-like stimulants are seen for scales and items assessing elevated mood, energy and alertness. Commonly abused drugs, an 'amphetamine-like' scale was developed for the Addiction Research Centre Inventory (ARCI) including items such as 'feeling more excited' and 'having a sharper memory' (Martin et al., 1971). Subjective effects are typically assessed using simple visual analogue scales or assessments such as the Profile of Mood States (POMS) and ARCI, which are often employed to discriminate between drugs in terms of their stimulant effect and/or abuse liability (Schuh et al., 2000).

Effects on Sleep Latency

D-amphetamine has been shown to reverse the shortening of sleep latency which occurs in sleep deprived healthy volunteers, in a dose dependent fashion (Newhouse et al., 1989). Furthermore, methylphenidate can prolong latency to sleep in healthy volunteers under both normal laboratory conditions and following sleep deprivation (Bishop et al., 1997).

Effects on Waking EEG/fMRI

Amphetamine suppresses sleep-deprivation related increases in low frequency (0.5–7 Hz) bands and also changes the circadian rhythm of other frequency bands in healthy volunteers during sustained wakefulness (Chapotot et al., 2003). Alone, EEG may not be a sensitive or reliable tool to assess amphetamine effects in normal healthy volunteers (Slattum et al., 1996). However, amphetamine does appear to influence event related potentials such as pre pulse inhibition following an auditory tone (Kroner et al., 1999) and the increases in amplitude of the 'cognitive' P300 that accompanies improved attention task reaction times in attention deficit disorder (Lopez et al., 2004). These kinds of evidence have given support to a role for dopaminergic dysfunction in schizophrenia and ADHD, and also the possible mechanisms by which amphetamine-like stimulants may improve attention in ADHD. A preliminary fMRI study in narcoleptics has shown that stimulants are able to reverse the reduction in regional cerebral activation associated with performance of a working memory task (Thomas, 2005).

Effects on Vigilance and Cognition

As discussed previously, some of the earliest psychomotor/vigilance task performance work identified the effect of d-amphetamine in attenuating vigilance decrement (the reduction in performance over the duration of the task) (Mackworth, 1965). DA is now widely considered to play a key role in the regulation of cognition and attention (Willner and

Scheel-Kruger, 1991, Nieoullon, 2002). Furthermore, dysfunction of the DA system may underlie cognitive deficits in various forms of dementia, schizophrenia, and ADHD, all of which have shown ameliorative action of DA agonists or antagonists (Court et al., 2000, Nieoullon, 2002, Siever et al., 2002). In Parkinson's disease (PD) in particular, DA pathology is the primary neurological hallmark of the disease and function of DA pathways may be severely compromised. The cognitive changes most associated with PD are those of executive dysfunction and memory/visuospatial impairment. Executive function may be broadly characterised as the ability to plan and organise goal-directed behaviours, and attention is considered to be a central element of this. PD patients demonstrate performance deficits on several tasks believed to be dependent upon forms of attention, such as the Stroop colour-word test and the trail-making task, and DA dysfunction has been clearly linked to these deficits (Kaasinen and Rinne, 2002). Pharmacotherapy for PD has included anti-cholinergic drugs, which may disrupt cognition and cause sedation, and also dopamine agonists or levodopa/carbidopa, which may disrupt sleep, particularly through nightmares, emergence of insomnia, but also daytime sedation. However, sleep-wake disorders may also be a primary manifestation of the disease itself and a target of new treatment strategies (Friedman et al., 2007).

Modafinil/Armodafinil

Modafinil (provigil) was the first in a new class of wake-promoting agents. Originally approved by the Food and Drug Administration (FDA) in 1998 for the treatment of EDS associated with narcolepsy, it has since been approved for the treatment of EDS associated with OSAHS and SWSD. Armodafinil (nuvigil) is the longer half-life enantiomer of modafinil. Following three recent large scale Phase III studies of armodafinil, employing mean sleep latency from the Multiple Sleep Latency Test (MSLT) and the Clinical Global Impression of Change (CGI-C) rating as the co-primary endpoints, the FDA also approved armodafinil for improving wakefulness in patients with EDS associated with OSAHS, narcolepsy and SWSD. Secondary endpoints on these studies included a cognitive test battery (CDR system), Epworth Sleepiness Scale (ESS), patient diary data, and the Brief Fatigue Inventory (BFI), which also showed some positive treatment effects, which will be discussed in more detail below. Whilst modafinil and armodafinil may act on a number of neurotransmitter systems including adrenergic (Duteil et al., 1990), GABAergic and serotonergic systems (Ferraro et al., 1996, Tanganelli et al., 1992), as with the amphetamine-like stimulants, they also have influences on DA (Wisor and Eriksson, 2005, Murillo-Rodriguez et al., 2007). In contrast, there may be far less potential for euphoric effects and abuse (Rush et al., 2002) and they may even have some efficacy in treatment for cocaine addiction (Karila et al., 2007). However, they are probably not entirely free from subjective stimulant effects (O'Brien et al., 2006). It is possible that this more specific action for wake-promotion, without the additional effects associated with the amphetamine-like stimulants, is related to a specificity for particular brain structures, resulting in a more targeted effect (Silvestri et al., 2002, Engber et al., 1998).

Self-reported Effects

Subjectively, in healthy non-sleep-deprived adults modafinil has been shown to increase ratings on 'amphetamine' and 'morphine-benzedrine' scales and reduce ratings on the 'pentobarbital-chlorpromazine-alcohol' scale of the ARCI. It has also been shown to increase 'vigour' ratings on the POMS and reduce 'sleepiness' on a VAS scale. This has some clear parallels with the effects of d-amphetamine, but modafinil did not increase 'drug-liking' and 'stimulation' ratings in the same way (Makris et al., 2007). In sleep-deprived healthy volunteers, although performance measures and sleep latencies were improved by modafinil (and caffeine and d-amphetamine), data from the Stanford Sleepiness Scale were equivocal (Wesensten et al., 2005), though subjective effects have been seen with visual

analogue scales (Lagarde et al., 1995). In patient studies, armodafinil has been shown to improve ratings of wakefulness on the ESS and reduce fatigue (Brief Fatigue Inventory) in OSAHS (Hirshkowitz et al., 2007, Roth et al., 2006) and narcolepsy (Harsh et al., 2006).

Effects on Sleep Latency

Sleep latencies have also been shown to be positively influenced in the above listed studies of modafinil and armodafinil, with positive effects seen following sleep deprivation and in disorders of EDS (Harsh et al., 2006, Hirshkowitz and Black, 2007, Hirshkowitz et al., 2007, Lagarde et al., 1995, Makris et al., 2007, Roth et al., 2006, Wesensten et al., 2005).

Effects on Waking EEG/fMRI

Modafinil decreases the rebound phenomenon in EEG slow-wave activity associated with sleep deprivation and the wake-promoting effects of modafinil appear to involve EEG activity which is distinct from that of d-amphetamine (Chapotot et al., 2003). EEG mapping may also be used to identify the decrement in vigilance associated with narcolepsy and its correction following modafinil treatment and this may be a more sensitive technique than either sleep latency (MSLT) or the subjective wakefulness (ESS) (Saletu et al., 2005). Functional scanning has revealed effects on brain activation of both overnight sleep deprivation and modafinil, with interactions revealing an ability of modafinil to counter adverse effects of sleep deprivation on working memory task performance at a moderate difficulty (Thomas and Kwong, 2006).

Effects on Vigilance and Cognition

An expanding literature exists detailing the effects of modafinil and armodafinil on measures of psychomotor vigilance and cognition. As expected, psychomotor vigilance tasks have frequently been employed in the study of the wake-promoting effects of these drugs and positive effects have been seen with several measures in healthy volunteers both sleep-deprived and non-sleep-deprived, and in patients (Harsh et al., 2006, Hirshkowitz and Black, 2007, Hirshkowitz et al., 2007, Lagarde et al., 1995, Makris et al., 2007, Roth et al., 2006, Wesensten et al., 2005). However, there are also a number of studies which suggest that modafinil and armodafinil may have direct pro-cognitive effects beyond improved psychomotor vigilance associated with an increase in wakefulness. Evidence has been seen for improvements in aspects of executive function: attentional set-shifting in schizophrenia (Turner et al., 2004b); response inhibition in adult ADHD (Turner et al., 2004a); and for improved memory in EDS: improved recall and recognition in OSAHS (Hirshkowitz et al., 2007); and improved recall and recognition in narcolepsy (Harsh et al., 2006). These findings may represent specific pro-cognitive effects associated with the particular actions of the drugs, or could be secondary to improved vigilance/wakefulness and this is a focus of future research. However, animals studies showing complex effects not only on attention, but also on various aspects of learning and memory, as well as pharmacological challenge studies and other cognitive models, do suggest primary cognitive effects (Witkin and Nelson, 2004).

Nicotine

Smokers smoke cigarettes predominantly due to an addiction to nicotine (Physicians, 2000). Smoking and intravenous nicotine produce feelings of relaxation, and there are dose dependent increases in drug "liking" and elevated scores on the Morphine-Benzedrine Group (or Euphoria) scale of the Addiction Research Center Inventory (Henningfield et al., 1985). Anecdotally, smokers report that smoking helps them to relax and cope with difficult situations, gives them confidence, overcomes boredom and fatigue, or produces feelings of satisfaction. The nicotinic receptors are one of two main types of cholinergic receptor

(nicotinic and muscarinic). Whilst studies show evening nicotine administration may disrupt REM sleep and result in earlier waking (Gillin et al., 1994) and that there are alerting and vigilant attention enhancing properties, wake-promoting effects have not been widely studied. However, despite a subjective anti-fatigue effect of nicotine, nicotinic receptors have thus far not been a target for drug development in sleep medicine and it is notable that there may be differential effects of nicotine depending upon dose i.e.: relaxing/sleep promoting at low doses; arousing/wake-promoting at higher doses. Interestingly, smoking cessation results in disturbed sleep suggesting there is not a simple relationship between tobacco use and wake-promotion (Staner et al., 2006). Nicotinic and muscarinic receptor agonists are currently being investigated in a number of indications associated with impaired cognition e.g. AZD3480 (AD, ADHD and schizophrenia (Dunbar et al., 2007a)) and xanomeline in schizophrenia (Shekhar et al., 2008).

Self-reported Effects

Subjective effects of nicotine include increased self-ratings of alertness (Griesar et al., 2002) as well as changes in 'drug-like' ratings associated with abuse liability and dependence (Henningfield et al., 1985). However, studies evaluating effects of nicotine on self-reported sleep scales such as the SSS or ESS are not prominent in the literature. It is not clear then how far subjective increases in alertness and reductions in fatigue might influence ratings on this type of scale.

Effects on Sleep Latency

Studies of abstinence from smoking show a reduction in sleep latency (MSLTs) over the day alongside increases in subjective withdrawal symptoms such as irritability (Prosser et al., 1994). Alongside evidence for earlier waking with evening nicotine (Gillin et al., 1994) a possible wake-promoting effect is suggested. However, formal studies of waking sleep latency/maintenance of wakefulness are not reported. Therefore, it is not clear if nicotine might directly influence these types of measure.

Effects on Waking EEG

In an early review of the effects of smoking on EEG, Conrin concludes that the evidence indicates obvious changes in EEG activity supporting arousal effects (Conrin, 1980). Later studies have shown an increase in EEG power in higher frequency bands (Gilbert et al., 2000, Griesar et al., 2002) and a relationship between cognitive benefits and EEG parameters for nicotine (Mansvelder et al., 2006) and receptor subtype selective nicotinic agonists (Dunbar et al., 2007a).

Effects on Vigilance and Cognition

Early work into the effects of nicotine on cognition has now been extensively replicated, and it is widely accepted that nicotine improves various aspects of human attention and information processing (Mansvelder et al., 2006). Drug development for cognitive disorders has focused on a number of nicotinic mechanisms with a view to providing cognition enhancement without unwanted (e.g. cardiovascular) side-effects. Recent trials of $\alpha 7$ nicotinic agonists (e.g. GTS-21 (Kitagawa et al., 2003), MEM-3454 [company website/press releases]) have shown that besides enhancing attention in volunteers, these compounds may also improve aspects of episodic memory. A similar profile of effects has emerged from trials with $\alpha 4\beta 2$ nicotinic agonists (e.g. TC-1734/AZD-3480 (Dunbar et al., 2007a)). Importantly, early work from Phase I safety and tolerability trials has since been replicated in clinical populations including adult ADHD, AAMI, schizophrenia and AD (Wilens and Decker, 2007, Ochoa and Lasalde-Dominicci, 2007, Dunbar et al., 2007b, Vellas et al., 2005).

Caffeine

Caffeine is undoubtedly one of the most widely used stimulant and wake-promoting drugs in the world. Mean consumption has been estimated to be 3mg/kg/day per person in the US and in the UK caffeine intake is higher at 4mg/kg, approximately 210 and 280mg respectively (Barone and Roberts, 1996). More recently a study of 1994–1996 and ongoing 1998 US Department of Agriculture survey data showed 87% of respondents consumed caffeinated food and drink and that average intake was 193 mg per day/1.2mg/kg, with increasing consumption with increasing age (Paganini-Hill et al., 2007). Large numbers of studies have investigated the effects of caffeine on various measures associated with wakefulness and it is thought that caffeine may exert these psychostimulant effects via antagonism of the adenosine receptors, thus increasing cortical cholinergic activity (Carter et al., 1995). Arousal effects may be attributed specifically to the A2A receptors as opposed to the A1 receptors (Huang et al., 2005). However, a further mechanism, blockade of adenosine receptors on GABA neurons, which reinforces inhibition of sleep-promoting neurons, may also play a role (Strecker et al., 2000). Striatal adenosine-dopamine receptor-receptor interaction is also believed to be important to psychostimulant effects of caffeine (Fisone et al., 2004).

Self-reported Effects

Following administration of caffeine, increases in subjective tension, nervousness and jitteriness have been seen (Loke, 1988, Zahn and Rapoport, 1987), but also decreased boredom (Loke, 1988) and mental fatigue, and increased alertness (Haskell et al., 2005). Importantly, these effects may also be seen with ‘naturalistic’ consumption of tea and coffee (equivalent to 4 and 8 servings per day) versus water (Hindmarch et al., 2000). This supports the assumption that these positive subjective effects are important to caffeine consuming behaviour. There is still a debate in the literature regarding the nature of effects on habitual and non-habitual caffeine consumers and the role that caffeine withdrawal may play. However, effects of caffeine are evident in non-habitual users (Childs and de Wit, 2006) and it is likely that effects are simply more pronounced in heavier users (Attwood et al., 2007, Christopher et al., 2005, Haskell et al., 2005).

Effects on Sleep Latency

As early as 1979 caffeine was identified as increasing latency to sleep in healthy volunteers, following night time awakenings (Bonnet and Webb, 1979). It has since been shown that 250mg caffeine administered in the morning and early afternoon prolongs sleep latency across the day (assessed with MSLTs at 1000, 1200, 1400, and 1600) in healthy male volunteers, versus placebo (Zwyghuizen-Doorenbos et al., 1990). These effects do not appear to be dependent on duration of sleep the previous night, as they occur in non-sleep restricted volunteers (Rosenthal et al., 1991). This increase in latency to sleep provides objective support for the subjective effects of caffeine, suggesting that ‘normal’ doses of caffeine in tea, coffee and cola drinks are capable of prolonging sleep latency in healthy subjects.

Effects on Waking EEG

Effects on waking EEG have also been seen to be consistent with a wake-promoting effect of caffeine. For example, Landolt et al. and Retay et al. have both shown sleep deprivation-induced increases in theta activity to be attenuated by 200mg caffeine in healthy volunteers (Landolt et al., 2004, Retey et al., 2006). However, the effects of caffeine on waking EEG in non-sleep deprived healthy volunteers, does not appear to have been studied and neither has more naturalistic caffeine consumption.

Effects on Vigilance and Cognition

A large number of studies have investigated effects of caffeine on vigilance and other aspects of cognitive function. Caffeine appears to exert its cognitive effects primarily through enhanced alertness and vigilant attention (Lieberman et al., 1987). However, caffeine may also have some direct effects on memory. Riedel et al. found 250mg of caffeine was able to attenuate scopolamine induced impairment of memory (Riedel et al., 1995). However, other studies have reported no direct memory effects (Loke, 1988), or have associated positive memory effects with counter-acting caffeine withdrawal (Hogervorst et al., 1999). In the latter study it was hypothesised that increased caffeine use in older cohorts may reflect self-medication for increasing cognitive deficits. Whilst lower acute doses (100mg) have been reported as having no effect on cognition (digit span, word learning, Stroop Word Colour test and Memory Scanning) (Schmitt et al., 2003), other studies report both acute and more sustained effects of 37.5 and 75mg caffeine as tea and coffee, on critical flicker fusion (a psychophysical threshold indexing arousal) and a choice reaction time task (assessing attention) (Hindmarch et al., 2000). More recently, Haskell et al. identified positive effects of 75 and 150mg on performance (reaction time and sentence verification), which were more pronounced in habitual non-consumers (the opposite being seen) for self-rated effects, whilst Hewlett et al. conclude that caffeine has dose dependent effects which are not due to withdrawal effects (Hewlett and Smith, 2007). Therefore, evidence for direct dose dependent effects of caffeine on attention/vigilance appears fairly robust. However, evidence for direct effects on other aspects of cognition such as learning and memory appears less strong.

Histamine (H₃) Receptor Antagonists

A recent target for both wake-promotion and cognition enhancement has been the histamine H₃ receptor (Parmentier et al., 2007, Passani et al., 2004). The known importance of histaminergic systems in the sleep-wake cycle (Pace-Schott and Hobson, 2002a) suggest histaminergic receptors as a potential target for pharmacotherapy and accumulating evidence suggest that H₃ receptor antagonists may be efficacious for both cognitive and sleep-wake disorders (Witkin and Nelson, 2004). These effects may be mediated through a number of interactions with other neurotransmitter systems relevant to sleep-wake and cognition, including acetylcholine, but may be free of stimulant effects associated with other compounds and in particular are not associated with an increase extracellular DA in rat brain (Bonaventure et al., 2007). However, whilst pre-clinical evidence has identified effects in animals models for cognition and wake-promotion (Komater et al., 2005, Komater et al., 2003, Giovannini et al., 1999, Blandina et al., 1996, Barbier et al., 2004), clinical research is at an early stage. Currently clinical trials with H₃ antagonists include GSK239512 for cognition, GSK189254 for narcolepsy and JNJ-17216498 for narcolepsy, but data from these studies are not yet published. However, a poster presentation by Vermeeren et al from Maastricht University has shown electrocortical arousal and a trend towards improved Mackworth Clock vigilance performance in man, with the H₃ antagonist betahistine (Vermeeren et al., 2006).

Sedative/hypnotics and sleep promoting drugs

An additional class of drugs which may be used in wake-promotion are those which improve sleep. The use of these drugs, such as ramelteon (Table II), is intended to normalise sleep and may thus improve wakefulness by reducing or illuminating the effects of disturbed sleep. Those same assessments which can be employed to assess the wake-promoting effects of the drugs can equally be used to assess the indirect wake-promoting effects of these sleep agents. However, whilst drug developers might be concerned to ensure a wake-promoting agent did not have properties resulting in disturbed sleep, a major issue for sleep promoting

drugs is to ensure the absence of 'hangover' effects following their use (Vermeeren, 2004). This is a topic which has been extensively considered in the past and the effects of the large numbers of sleep agents on daytime wakefulness is not a topic which will be considered in detail in the present review. However, it is clear that many of the same techniques used to measure changes in wakefulness following treatment with (putative) wake-promoting drugs, might equally be applied to the assessment of daytime sedation/hangover effects following prior use of sedative hypnotic drugs.

Discussion

It is clear then that a number of techniques can be applied to the measurement of wake-promoting effects. Subjective assessments are able to discriminate clinically relevant levels of sleepiness in EDS and are sensitive to treatment related improvements in patients. In addition, a range of items allow for differentiation between wake-promotion and other potential properties of wake-promoting drugs, including problematic euphoria and abuse liability. However, evidenced through their lack of use, simple scales for rating sleepiness such as the ESS and SSS may be relatively insensitive in early phase research in healthy volunteers, who are unlikely to be experiencing sleepiness unless sleep deprived. Therefore, they are unsuited to measuring early indications of efficacy or for hypothesis generation. Furthermore, subjective assessments alone are not good at differentiating levels of sedation and require the addition of objective psychomotor performance assessments (Shamsi and Hindmarch, 2000, Harrison and Wesnes, 2006). Thus the same may be expected of wakefulness.

Sleep latency assessment provides a sound technique for measuring objective levels of wakefulness, and is sensitive to both clinical EDS and effective pharmacotherapy. In clinical trials, alongside clinician ratings, this measure provides a primary efficacy outcome. However, it is again unsuited to the assessment of non-sleep deprived healthy volunteers. In contrast, both brain scanning techniques and cognitive assessment may provide measures which are applicable to all stages of the drug development process. Both provide measures which are sensitive to drug effects in normal volunteers, as well as sleep-deprived and clinical populations. At early phase, they may be used as surrogate markers for wake-promoting effects for hypothesis generation and proof of concept, but also may provide a dual role in suggesting efficacy for cognitive indications also. At phases II and III these assessments may provide supportive efficacy and mechanistic information. However, the implications of improved cognition for quality of life and as an outcome in itself should not be ignored in conditions where cognitive impairment is associated with EDS, or vice versa. Furthermore, it is not only attention (psychomotor vigilance), which should be a target for cognition assessment. As we have seen, wake-promoting agents and disorders of and associated with EDS have the potential to influence wider aspects of cognition. Therefore, use of broader cognition batteries assessing aspects of function such as working and episodic memory and executive function is warranted and is commonly, though not routinely, employed. These assessments may provide an indication of possible direct cognitive effects, as well as those that may be secondary to increases in wakefulness.

The overlap in both the underlying neurobiology of; and the techniques of subjective and objective assessment of wakefulness, strongly supports the likelihood that both kinds of effects may be seen with a potential wake-promoting agent. However, it is also possible that both areas of function may be influenced independently by drug treatment. The H3 antagonists provide a clear example of this, with compounds in development both as wake promoting agents and as cognition enhancers, and a similar direction could be expected for modafinil/armodafinil, currently registered only for the treatment of EDS, but which have shown potential to enhance various aspects of cognition. Therefore, it important not only to

assess wake-promoting drugs for their potential to influence aspects of cognition, but also to consider the possible effects on sleep-wake processes of nootropic drugs.

Conclusions

Wake-promotion, but also cognition may be measured in similar ways, and both areas of behavior also have similarities in their underlying neurobiology. Excessive sleepiness and cognitive dysfunction co-occur in a large number of disorders and may be related through underlying disease pathology and pharmacotherapy. Wake-promoting drugs have nootropic potential and vice versa. Cognition assessments may act as both surrogate markers and supportive efficacy endpoints for wake-promoting effects, but also as proof of concept and efficacy outcomes in their own right. It is prudent in the development of wake-promoting drugs and also sedative hypnotics to screen broadly for potential to influence aspects of cognition thus, providing information for hypothesis generation/therapeutic potential, safety/potential for hangover effects, proof of concept and efficacy.

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Table I

Commonly used assessments of wake-promoting effects

Domain of assessment	Assessment	Brief description
Clinical assessment	Clinical assessment and diagnosis	The clinicians' global impression (CGI) is an outcome of primary importance in sleep medicine as in other areas of clinical research. The importance of thorough diagnosis and medical history taking should not be under-estimated. Existing use of medications may be an underlying cause of EDS, so must form part of any clinical evaluation (Guilleminault and Brooks, 2001).
Patient reported outcomes - for a review see Devine et al., 2005 (Devine et al., 2005)	Epworth sleepiness scale (Johns, 1991)	The ESS is a self-administered questionnaire used to measure levels of daytime sleepiness. Subjects score 8 situations from 0 to 3. A score of 10 or more is considered sleepy, a score of 18 or more very sleepy. The scale is sensitive to differences in primary snoring, OSAHS, narcolepsy, idiopathic hypersomnia, insomnia and periodic limb movement disorder (PLMD) (Devine et al., 2005).
	Leeds sleep evaluation questionnaire (Parrott and Hindmarch, 1980)	The LSEQ assesses the ease of getting to sleep (GTS), quality of sleep (QOS), ease of awakening from sleep (AFS) and alertness and behavior following wakefulness (BFW), using ten 100mm visual analogue scales. The scale has shown sensitivity to improvements in sleep following anti-depressant treatments (Sechter et al., 1999, Dorman, 1992) and to lorazepam Vs clonazepam (Hindmarch and Gudgeon, 1980).
	Pittsburgh sleep quality index (Buysse et al., 1989)	The PSQI is a self-rated questionnaire assessing sleep quality and disturbance over 1-month in clinical/psychiatric populations. The 19 items generate 7 component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction; and one global score. The scale is sensitive to differences in depression, sleep disturbance, somnolence, melatonin and anti-depressants (Devine et al., 2005).
	Stanford sleepiness scale (Hoddes et al., 1972) and Karolinska sleepiness scale (Gillberg et al., 1994)	The SSS is a 7 point scale to assess self-reported alertness at the present time. The scale ranges from 1 (most alert) to 7 (almost asleep). The scale has been shown to be sensitive to OSAHS, narcolepsy and sleep deprivation (Johns, 1992, 1998, Hoddes et al., 1972). The KSS is a similar widely used instrument.
	St. Mary's Hospital sleep questionnaire (Ellis et al., 1981) and similar longitudinal questionnaires and sleep diaries	The SMHSQ is a self-rated questionnaire assessing the previous night's sleep; designed for repeated use by hospital patients. It measures time to fall asleep, duration of sleep, depth of sleep, awakenings during sleep, sleep quality, clear-headedness on waking and sleep satisfaction. The scale was sensitive to differences in sleep quality in patients undergoing surgery (Devine et al., 2005). The Pittsburgh sleep diary is a similar instrument (Monk et al., 1994). Additionally, both clinical and research sleep laboratories employ a wide variety of customized sleep diaries.
Latency to sleep	Maintenance of wakefulness test (Doghramji et al., 1997)	The MWT measures how long it takes a subject to fall asleep whilst sitting in a quiet and dimly lit room and attempting to stay awake with eyes open. Duration is fixed at 20 or 40 minutes and the outcome measure is a mean of 4 or more naps across the day.
	Multiple sleep latency test (Carskadon et al., 1986)	The MSLT measures how long it takes a subject to fall asleep whilst lying down in a darkened room, and is typically reported as the mean of 4 to 6 naps taken at two hourly intervals over the day.
Psychomotor/Vigilance	'Pen and Paper' Neuropsychological Tests	There are a large number of pen and paper based assessments designed to measure aspects of psychomotor speed and vigilant attention (e.g. DSST, Digit cancellation, SDMT, Trails A, etc). Essential principles typically involve elements of timed/speeded responding, visual search and motor response.
	Computerized Tests	Based on early automated tests such as the Mackworth Clock task (Mackworth, 1961), there are also a profusion of computerized psychomotor vigilance tasks. The most common of these in sleep research is the PVT (Dinges and Powell, 1985), which requires sustained attention to a variable visual stimulus over a set period (e.g. 10 or 20 minutes). The PVT has been tested in a number of conditions recognized to result in cognitive deficits related to sleep loss, including total sleep deprivation, chronic partial sleep deprivation, sleep fragmentation, and disorders of excessive sleepiness (Lim and Dinges, 2008, Kim et al., 2007). A number of other vigilance tasks as well as tests of simple and choice reaction time may be employed in a similar way.

Domain of assessment	Assessment	Brief description
	Driving and flight simulators	There are a number of simulators of driving, flight and other types of skilled task performance in use for transport and human factors research, some of which have also been utilized in clinical drug trials. Performance is typically measured by skilled raters or via abstracted measures (e.g., lane deviations) comparable to other assessments of psychomotor vigilance.
Behavioral, electrophysiological and functional neuroimaging techniques	Behavioral measures	Actigraphy provides data on movement (typically a wrist worn device), with frequent sampling over a number of days or weeks. These data can differentiate sleep from wakefulness and thus disturbed sleep (Sadeh et al., 1994, Jean-Louis et al., 1997), but may also be used to provide information on the level or intensity of activity during wakefulness and are thus sensitive to the day time effects of reduced sleep on the preceding night (Roehrs et al., 2000). This technique may then be used to make inferences about the level of wakefulness, for example in the evaluation of stimulant medication in narcolepsy (Bruck et al., 2005), but may also be used to make inferences regarding cognitive factors such as volition, motivation, apathy and hyperactivity e.g. apathy in traumatic brain injury and volition in schizophrenia (Muller et al., 2006, Farrow et al., 2006).
	Electrophysiological measures: laboratory and ambulatory polysomnography	PSG may be used to measure EEG, eye movements (EOG), muscle activity or skeletal muscle activation (EMG) heart rhythm (ECG), respiratory airflow, respiratory effort and peripheral pulse oximetry. Ambulatory PSG allows for the assessment of daytime sleep in addition to night-time sleep with the application of 24 hour PSG as well as assessment outside of a laboratory setting (Erwin and Marsh, 1990).
	Electrophysiological measures: (waking) Electroencephalography (EEG); Event related potentials (ERPs); Event related fields (ERFs); Magnetoencephalography (MEG)	Waking EEG may be used to more directly index arousal/wakefulness. EEG power in the theta frequency band (5–8 Hz) during quiet waking increases during sleep deprivation in healthy controls, and this is predictive of the subsequent homeostatic increase of sleep slow-wave activity (EEG power between 0.5 and 4.0 Hz) (Cajochen et al., 1995). This indicates theta power during waking reflects the rise in sleep propensity and may be used as an EEG measure indexing declining wakefulness. In narcolepsy the power density in the 11–12.5 Hz (high alpha–low beta) bands during waking has also been seen to be lower in primary versus secondary narcolepsy, perhaps reflecting lower arousal (Honma et al., 2000). There may also be differences in homeostatic sleep pressure between shorter and longer sleepers (Aeschbach et al., 2001). In OSAHS EEG slowing and a greater activity in delta, theta and beta bands following sustained wakefulness is seen versus healthy controls (Greeneche et al., 2008, Mathieu et al., 2007). Thus there are aspects of waking EEG data which may be used to index wakefulness or propensity for sleep. As with the performance measures described above, EEG techniques may also be used to investigate cognition its disorders and its interactions with sleep and sleepiness using ERPs and ERFs. ERP and ERF components show specific relationships with cognitive processes (Hillyard and Kutas, 2002) knowledge of which can be used to investigate the effects of sleep and its disruption on cognitive processes (Colrain and Campbell, 2007).
	Functional neuroimaging	Studies have shown greater BOLD (blood oxygen level dependent) response in bilateral prefrontal cortex and parietal lobes during cognitive task performance thought to reflect compensation to detrimental effects of sleep deprivation (Drummond and Brown, 2001). More recently studies have been conducted in clinical populations -for a brief review see Chauh & Chee, 2008 (Chuah and Chee, 2008).

Table II

Ongoing clinical trials of wake-promoting effects

Nature of study	Study drug (s)	Title	Relevant outcomes
Direct assessment of wake-promoting effects	Armodafinil	A Randomized Placebo- Controlled Trial of Armodafinil (Nuvigil) for Fatigue in Patients With Malignant Gliomas (NCT00766467)	Fatigue
	Armodafinil	Effectiveness of Armodafinil for Treating Fatigue in Adults With HIV/AIDS (NCT00737204)	Fatigue severity scale; Role function scale; Cognitive function
	Armodafinil	Armodafinil for Fibromyalgia Fatigue (NCT00568919)	Fatigue severity scale
	Armodafinil	Study of the Effect of Armodafinil Treatment in Healthy Subjects With Excessive Sleepiness Associated With Jet Lag Disorder (NCT00758498)	MSLT; KSS
	Armodafinil	Study to Evaluate the Efficacy and Safety of Armodafinil as Treatment for Adults With Excessive Sleepiness Associated With Obstructive Sleep Apnea/Hypopnea Syndrome With Comorbid Major Depressive Disorder or Dysthymic Disorder (NCT00518986)	MWT; ESS
	Armodafinil	An Eight Week, Double-Blind Efficacy Study of Armodafinil Augmentation to Alleviate Fibromyalgia Fatigue (NCT00678691)	Brief fatigue inventory
	Armodafinil	Sleepiness and Brain Function: The Effect of Armodafinil in Shift Work Sleep Disorder (NCT00688142)	ERPs
	MK0249 (Merck, H3 agonist); Modafinil	Treatment of Refractory Excessive Daytime Sleepiness in Patients With Obstructive Sleep Apnea/Hypopnea Syndrome (OSA/HS) Using Nasal Continuous Positive Airway Pressure (nCPAP) Therapy (NCT00620659)	Wake-promotion
Assessment of wake promoting effects secondary to improved sleep parameters	Ramelteon	Ramelteon Night Shift Study (NCT00595075)	Neurobehavioral performance battery
	Ramelteon	Ramelteon (ROZEREM) in the Treatment of Sleep Disturbances Associated With Parkinson's Disease (NCT00462254)	ESS; Sleep disorder questionnaire; Hopkins verbal learning task
	Ramelteon	Ramelteon for Treatment of Adult Patients With ADHD- Related Insomnia (NCT00622427)	CGI (day time functioning mentioned without reference to specific assessments)
	Ramelteon	Efficacy and Tolerability of Ramelteon in Patients With Rapid Eye Movement (REM) Behavior Disorder and Parkinsonism (NCT00745030)	Sleep diary; CGI; ESS; PSQI; Fatigue Severity Scale; Mini Mental State Exam; Montreal Cognitive Assessment Scale
	Ramelteon	A Multicentre, Randomised, Double-Blind, Double- Dummy, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Ramelteon Compared to Placebo With Zopiclone as a Reference Arm in Adults With Chronic Insomnia (NCT00237497)	Sleep and daytime function questionnaires; DSST; memory recall
	Ramelteon	Improving Sleep in Nursing Homes (NCT00576927)	Daytime sleep, activity and behavior; Actigraphy

Nature of study	Study drug (s)	Title	Relevant outcomes
	Ramelteon	Functional Melatonin Replacement for Sleep Disruptions in Individuals With Tetraplegia (NCT00507546)	Daytime alertness

Searches conducted in clinicaltrials.gov December 2008 using the terms “alerting”, “wake promoting”, “wakeful” and wakefulness” – then additional review of drugs included in search results to identify ongoing studies using assessment of wake promotion without specific mention of these terms.