BJP British Journal of Pharmacology

DOI:10.1111/bph.12261
www.brjpharmacol.org

Themed Section: Orexin Receptors

REVIEW

Discovery and development of orexin receptor antagonists as therapeutics for insomnia

C J Winrow and J J Renger

Department of Neuroscience, Merck Research Laboratories, West Point, PA, USA

Correspondence
John J Renger, Merck & Co., Inc., 770 Sumneytown Pike, WP42-209, PO Box 4, West Point, PA 19486-0004, USA.
E-mail: john_renger@merck.com

Keywords
orexin receptor antagonist; insomnia; GABA; sleep

Received
28 February 2013
Revised
13 May 2013
Accepted
16 May 2013

Insomnia persistently affects the quality and quantity of sleep. Currently approved treatments for insomnia primarily target γ-aminobutyric acid-A (GABA-A) receptor signalling and include benzodiazepines and GABA-A receptor modulators. These drugs are used to address this sleep disorder, but have the potential for side effects such as tolerance and dependence, making them less attractive as maintenance therapy. Forward and reverse genetic approaches in animals have implicated orexin signalling (also referred to as hypocretin signalling) in the control of vigilance and sleep/wake states. Screening for orexin receptor antagonists using *in vitro* and *in vivo* methods in animals has identified compounds that block one or other of the orexin receptors (single or dual orexin receptor antagonists [SORAs and DORAs], respectively) in animals and humans. SORAs have primarily been used as probes to further elucidate the roles of the individual orexin receptors, while a number of DORAs have progressed to clinical development as pharmaceutical candidates for insomnia. The DORA almorexant demonstrated significant improvements in a number of clinically relevant sleep parameters in animal models and in patients with insomnia but its development was halted. SB-649868 and suvorexant have demonstrated efficacy and tolerability in Phase II and III trials respectively. Furthermore, suvorexant is currently under review by the Food and Drug Administration for the treatment of insomnia. Based on the publication of recent non-clinical and clinical data, orexin receptor antagonists potentially represent a targeted, effective and well-tolerated new class of medications for insomnia.

LINKED ARTICLES
This article is part of a themed section on Orexin Receptors. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2014.171.issue-2

Abbreviations
DORA, dual orexin receptor antagonist; REM, rapid eye movement; SORA, single orexin receptor antagonist

Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, (American Psychiatric Association, 2000), insomnia is defined as difficulty initiating or maintaining sleep or non-restorative sleep for at least 1 month, which causes clinically significant distress or impairment in social, occupational or other important areas of functioning. This sleep disturbance should not occur exclusively during the course of narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep disorder, parasomnias or a mental disorder (e.g. major depressive disorder), or as a result of substance abuse or another medical condition. More commonly, this sleep disorder is classified as secondary (attributable to a medical or psychiatric cause) or primary insomnia (idiopathic or psychophysiological in nature) (Morgenthaler *et al.*, 2006). A main aim of treatment for insomnia is to improve sleep onset and, in particular, sleep maintenance without next-day 'hangover' effects. Currently available treatments primarily rely on the modulation of GABA-A receptor-mediated mechanisms, a therapeutic strategy that is helpful to many patients but also associated with central nervous system-related adverse events, for example morning sedation and cognitive hangover effects (Hindmarch *et al.*, 2006; Roth, 2007; Otmani *et al.*, 2008; Hoque and Chesson Jr, 2009; Roehrs and Roth, 2012). An idealized pharmacotherapy for the treatment of insomnia has been suggested by the British Association of Psychopharmacology (Figure 1) (Wilson *et al.*, 2010), and includes rapid sleep onset, with maintenance throughout the night, lacking next day impairment and minimal adverse effects.

As described previously in this special issue, the orexin signalling system (also called the hypocretin system) was discovered and characterized in rodent and dog

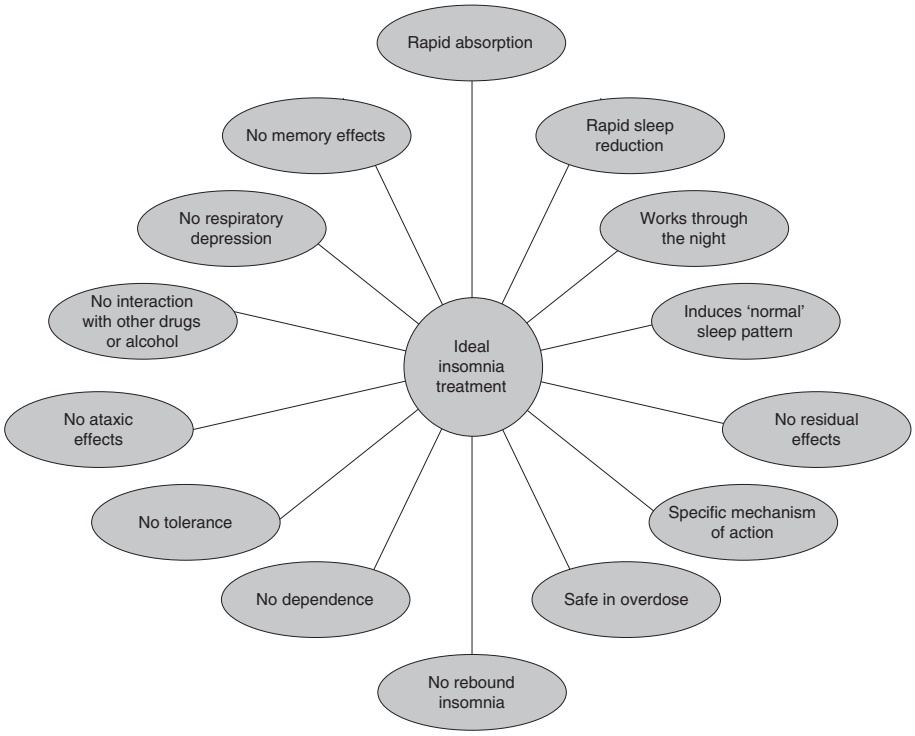

Figure 1

The characteristics of a hypothetical ideal insomnia treatment. Wilson *et al.*, J. Psychopharmacol (vol. no. 24, issue no. 11) pp. 1577–1601. © 2010 by Wilson *et al.* Reprinted by permission of SAGE (Wilson *et al.*, 2010).

models of narcolepsy, using both forward and reverse genetic approaches (de Lecea *et al.*, 1998; Sakurai *et al.*, 1998; Chemelli *et al.*, 1999; Lin *et al.*, 1999; Nishino *et al.*, 2000). The revelation of the genetic basis for regulation of sleep and wake by the orexin-signalling system has made modulation of orexin receptors an attractive target for pharmaceutical development of treatments for insomnia. Further, due to the remarkable level of genetic and functional conservation of the orexin system in mammals, there is a high level of translatability of efficacy from rodent to human (Brisbare-Roch *et al.*, 2007; Gotter *et al.*, 2012b) that has facilitated drug development.

Many new drug mechanisms fail during pharmaceutical development due primarily to a lack of efficacy. Targets with genetic validation have a higher probability of success but are rare (Renger and Kern, 2011). Understanding of the genetic basis of arousal governed by orexins provides a model system for the generation of proof of concept data and for the testing of novel small molecules for the treatment of insomnia. Furthermore, characterization of the orexin 1 and orexin 2 receptors (OX_1R and OX_2R) as G-coupled protein receptors (Sakurai *et al.*, 1998) facilitated the development of medications that could attenuate their activation and responses and consequently impact on sleep/wake control in the brain selectively.

Identification of novel medications for insomnia has relied upon *in vitro* assays and *in vivo* preclinical screens of libraries of molecules in order to identify compounds that selectively act on the target receptors. This review will discuss the development of orexin receptor antagonists to date and describe how some of these molecules are used to further delineate the function of the orexin receptors, with some proceeding through clinical development to become potential novel medications for the treatment of insomnia.

Orexin receptor antagonists identified by high-throughput screening

The orexin system plays a key role in promoting wakefulness across species. Orexin neuron activity oscillates throughout the day, with the greatest activity occurring during the normal wake period and falling silent during the normal sleep period (Taheri *et al.*, 2000; Zeitzer *et al.*, 2003; Grady *et al.*, 2006). In genetic studies in rodents and dogs, complete loss of orexin signalling over time results in fragmented sleep and arousal states but leaves the overall amounts of sleep and wake constant over a 24 h period (Hara *et al.*, 2001; Beuckmann *et al.*, 2004).

In patients with narcolepsy, post-mortem studies have shown very few surviving orexin-producing neurons and chronically reduced levels of orexin-A in their cerebrospinal fluid; these findings indicated that near complete loss of normal orexin signalling has a significant effect on consolidation of sleep and arousal in humans (Peyron *et al.*, 2000; Mignot *et al.*, 2002; Thannickal *et al.*, 2003; Crocker *et al.*, 2005). Clinically, narcolepsy is characterized by excessive daytime sleepiness and the occurrence of characteristic waking symptoms associated with disrupted rapid eye movement (REM) sleep, such as cataplexy (sudden loss of muscular

tone), sleep paralysis and hypnagogic (associated with the rapid transition to sleep) and hypnopompic hallucinations (associated with the transition from sleep) (Morgenthaler *et al.*, 2007).

The role of the individual orexin neuropeptides and of the orexin receptors in producing these effects is not fully understood. However, characterization of acute pharmacological blockade versus complete pathological loss of signalling is now being pursued via use of novel orexin receptor antagonists. Interestingly, to date, no group has reported a pharmacological recapitulation of the narcoleptic phenotype via pharmacological blockade of the orexin system (Brisbare-Roch *et al.*, 2007; Winrow *et al.*, 2011; Herring *et al.*, 2012b).

Single orexin receptor antagonists

The first small molecules identified during screening reportedly inhibited only single orexin receptors (single orexin-receptor antagonists; SORAs). Some of these, for example, SB-334867 (a heterocyclic urea developed by GSK that bound to OX_1R) and JNJ-10397049 (an OX_2R antagonist developed by Johnson & Johnson), have been used as receptor-specific probes. By inhibiting the activity of one receptor subtype in animal models, it was possible to observe how the absence of its downstream signal affected arousal and sleep architecture. In this way, studies using SORAs and/or rat knockouts indicated that arousal was primarily governed by OX_2R signalling while switching between vigilance states (and stages in sleep architecture) was primarily impacted by both receptors (Dugovic *et al.*, 2009; Gozzi *et al.*, 2011; Gotter *et al.*, 2012b).

There are potential complications when using these agents as orexin receptor probes. For example, since the selectivity of SB-334867 for OX_1R is only approximately 50-fold higher than that for OX_2R (Haynes *et al.*, 2000; Porter *et al.*, 2001), at higher doses, SB-334867 is likely to block both orexin receptors, complicating interpretation of results in high dose studies. In addition, SB-334867 has demonstrated binding activity with a number of other receptors and transporters (Winrow *et al.*, 2012a). Moreover, SB-334867 reportedly degrades when stored as a solution for use in preclinical *in vivo* and *in vitro* tests and can decompose to an inactive form when kept as a hydrochloride salt (McElhinny Jr *et al.*, 2012). These findings introduce a number of confounding effects to studies employing SB-334867 as a single receptor probe and caution should be used in interpreting data regarding the functional roles of individual receptors based on these studies alone.

Dual orexin receptor antagonists

Evidence from murine knockout models indicated that loss of prepro-orexin peptide (a precursor of both orexin neuropeptides) (Chemelli *et al.*, 1999) or orexin neurons (Hara *et al.*, 2001) results in a more robust sleep phenotype than loss of function of either one of the receptor subtypes alone. Therefore, development of orexin receptor antagonists for the treatment of insomnia has focused on inhibiting both receptor subtypes by the use of dual orexin receptor antagonists (DORAs). A number of DORAs have emerged from molecular screens across a variety of structural classes and several of these have progressed to clinical development as treatments for insomnia; to date, SORAs have not been reported to have reached clinical development.

Currently, the most widely discussed DORA molecules in the literature are SB-649868 (a piperidine amide) developed by GSK, almorexant (a tetrahydroisoquinolone) developed by Actelion, and suvorexant (MK-4305; a diazepane) and MK-6096 (a piperidine carboxamide) that have both been developed by Merck. Other classes of compounds with orexin receptor antagonist activity include pyrrolidine carboxamides, proline amides, diazaspirodecanes, indoles, heteroaryl piperidines, amidoethylthioether derivatives, sulfonamides, spirobenzodioxanes and acyclic diamines (Coleman and Renger, 2010).

Preclinical, pharmacological and pharmacokinetic data for selected orexin receptor antagonists

While numerous orexin receptor antagonists have been identified using screening techniques similar to those outlined above, most have not continued on to clinical development. These include both SORAs – EMPA (selectivity >900 greater for OX_2R over OX_1R), JNJ-1037049 (selectivity 630 times greater for OX_2R over OX_1R), GSK-1059865 (selectivity 79 times greater for OX_1R over OX_2R), SB-334867 (selectivity 50 times greater for OX_1R over OX_2R), SB-408124 (selectivity 64 times greater for OX_1R over OX_2R) and SB-674042 (selectivity 130 times greater for OX_1R over OX_2R) – and the DORAs, DORA-1 (selectivity 0.1-0.2 times greater for OX_2R over OX_1R), DORA-12 (selectivity 1.0–10.5 times greater for OX_2R over OX_1R) and DORA-22 (selectivity 3.2–15 times greater for OX_2R over OX_1R) (Smart *et al.*, 2001; Langmead *et al.*, 2004; McAtee *et al.*, 2004; Bergman *et al.*, 2008; Malherbe *et al.*, 2009; Cox *et al.*, 2010; Faedo *et al.*, 2012).

Pharmacological and pharmacokinetic data for the most widely described orexin-receptor antagonists – almorexant, DORA-22, MK-6096 (DORA-28), SB-649868 and suvorexant (MK-4305) – are summarized in Tables 1 and 2. With the exception of almorexant and DORA-22, all of these are in various stages of clinical development with suvorexant being the most advanced.

Characterizing orexin signalling

Early studies noted increased feeding behaviour secondary to arousal with exogenous administration of orexins in rodents. Research into the potential role of orexin signalling blockade in treating metabolic disorders has failed to progress and it is now thought that the effects of orexin on feeding may be subsequent to their role in arousal (Gotter *et al.*, 2012b). To date, pharmacological studies of novel orexin receptor antagonists in animals have not indicated a clear relationship with changes in feeding.

JNJ-10397049 (an OX_2R-specific SORA) decreased latency to sleep and locomotor activity and increased REM sleep, non-REM sleep and total sleep time in rats; SB-408124 (an OX_1R SORA) did not exhibit any of these effects (Dugovic *et al.*, 2009). Of note, when SB-408124 and JNJ-10397049 were co-administered, sleep induction and prolongation of non-REM sleep by the OX_2R-specific antagonist were partially attenuated while latency to REM sleep was shortened and

Table 1

Selectivity, binding affinities and dissociation constants for selected dual orexin receptor antagonists at human orexin receptors

Drug name	Stage of development	Selectivity	pK_i (binding affinity) (nM)	pK_b (dissociation constant) (nM)	References
Almorexant	No longer in development despite completion of Phase III trial RESTORA I	OX_2R 1.6X OX_1R	OX_1R: 2.7 OX_2R: 0.2	OX_1R: 128.4 OX_2R: 118.9	Brisbare-Roch *et al.*, 2007; Winrow *et al.*, 2012b
DORA-22	Preclinical development	OX_2R 3.2-15X OX_1R	OX_1R: 9.7 OX_2R: 0.6	OX_1R: 32 OX_2R: 10	Winrow *et al.*, 2012b
MK-6096	Phase II clinical trials	OX_2R 1.0-8.1X OX_1R	OX_1R: 2.5 OX_2R: 0.3	OX_1R: 11 OX_2R: 11	Winrow *et al.*, 2012b
SB-649868	Phase II trials	OX_2R 0.6-0.8X OX_1R	OX_1R: 9.5 OX_2R: 9.4	NA NA	Faedo *et al.*, 2012
Suvorexant (MK-4305)	Phase III trials (currently undergoing FDA review)	OX_2R 0.9-1.6X OX_1R	OX_1R: 1.2 OX_2R: 0.60	OX_1R: 50 OX_2R: 56	Cox *et al.*, 2010

FDA, Food and Drug Administration; NA, not available.

Table 2

Pharmacokinetics of selected dual orexin receptor antagonists. [a]Previously unpublished observations; [b]Apparent terminal t½

Drug name	Bioavailability (%)	T_{max} (h)	C_{max} (ng mL^{-1}; nM)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h mL^{-1}; μM*hr)	Refs
Almorexant						
Dog	18–49	0.5–2.0	NA	8.0–9.0	NA	Brisbare-Roch *et al.*, 2007; Hoch *et al.*, 2012c
Rat (100–300 mg·kg^{-1})	8–34	NA	NA	NA	NA	
Human (200 mg)	11.2	0.9	154.0	38.4	523.0	
DORA-22						
Dog (3 mg·kg^{-1})	NA	0.8	1140	2.5	4.6	Winrow *et al.*, 2012b
Dog (30 mg·kg^{-1})	NA	1.0	7300	2.5	64.3	
Rat (10 mg·kg^{-1})	32[a]	0.5[a]	670	0.5	2.5	
MK-6096						
Dog (0.25 mg·kg^{-1})	49	0.8	194	1.7	0.4	Coleman *et al.*, 2012; Winrow *et al.*, 2012b
Dog (0.5 mg·kg^{-1})	49	0.4	468	1.7	1.3	
Rat (15 mg·kg^{-1})	25	0.4	1900	0.5	2.3	
SB-649868						
Dog	NA	NA	NA	<1.0	NA	Renzulli *et al.*, 2011; Bettica *et al.*, 2012a
Rat	NA	NA	NA	<1.0	NA	
Human (30 mg)	NA	4.0	1200	4.8	8300	
Human (5 mg)	NA	2.5	158	3.5	NA	
Human (15 mg)	NA	2.5	624	4.8	NA	
Human (30 mg)	NA	3.0	964	5.1	NA	
Suvorexant						
Dog (3 mg·kg^{-1})	56	0.4[a]	817	3.3	4.0	Cox *et al.*, 2010; Winrow *et al.*, 2011; Sun *et al.*, 2013
Rat (10 mg·kg^{-1})	19	3.3[a]	1600	0.6	12.4	
Human (10 mg)	NA	3.0	440	9.0[b]	6.7	
Human (50 mg)	NA	3.0	870	10.8[b]	10.9	
Human (100 mg)	NA	3.0	2120	13.1[b]	29.8	

NA, not available.

REM sleep duration was slightly prolonged. Dugovic *et al.* interpreted their results to indicate that the two orexin receptor subtypes do not contribute equally to the modulation of arousal and shifts in sleep states and to also reflect the complex interactions that lead to sleep induction and arousal (Dugovic *et al.*, 2009).

In preclinical *in vivo* studies, administration of the DORA SB-649868 attenuated grooming activity evoked by injection of orexin A in rats. Moreover, in this study SB-649868 (3–30 mg·kg^{-1}) significantly reduced latency to and increased the duration of non-REM and REM sleep compared with placebo ($P < 0.001$ for all comparisons) (Di Fabio *et al.*, 2011). SB-649868 did not impair motor co-ordination in rats, whereas both zolpidem and ethanol were detrimental to motor performance and potentiated each other's effects. These results may indicate that zolpidem has broad downstream effects as a result of impacting global GABA signalling, while the effects of the orexin receptor antagonists are specific to arousal (Di Fabio *et al.*, 2011).

Almorexant, the first DORA reported to enter clinical development, demonstrated dose-dependent increases in REM and non-REM sleep, and decreased orexin A-induced locomotion in mice and rats (Brisbare-Roch *et al.*, 2007; 2008; Dugovic *et al.*, 2009; Li and Nattie, 2010; Mang *et al.*, 2012). By contrast, treatment of rats with the GABA-A receptor modulator zolpidem resulted in longer non-REM sleep but no prolongation of REM sleep (Brisbare-Roch *et al.*, 2007; 2008). Furthermore, almorexant did not induce sleep in knockout mice lacking orexin receptors, providing proof of concept for the mechanism of action of this compound (Mang *et al.*, 2012). Almorexant did not reduce next-day motor performance in a rat model of sedation and muscular relaxation, whereas rats given zolpidem or ethanol exhibited hangover effects, which were exacerbated when both of the latter agents were co-administered (Steiner *et al.*, 2011).

Pharmacokinetic studies with almorexant have revealed drug-drug interactions via CYP3A4 inhibition. Almorexant increased the maximum concentration, half-life and overall exposure of the benzodiazepine midazolam and increased the maximum concentration and overall exposure of the hypolipidaemic drug simvastatin (Hoch *et al.*, 2012b). A slight food effect (delayed time to maximum plasma concentration, higher overall exposure and prolonged half-life) has been reported when almorexant is taken with a high-fat meal; however, the authors of this study indicated that precaution need not be exercised with regard to almorexant and meal times (Hoch *et al.*, 2011b). In addition, no dose adjustment is required with almorexant when taken by Japanese patients compared with Caucasian individuals despite small differences in the pharmacokinetics of this DORA in these populations (Hoch *et al.*, 2011a).

Suvorexant reduced locomotor activity and promoted sleep in rats, dogs and rhesus monkeys in a dose-dependent manner (Winrow *et al.*, 2011). Retention of the sleep-inducing effects of suvorexant across multiple species in preclinical studies provided a strong scientific basis for pursuing the development of suvorexant as a therapy for insomnia.

MK-6096 significantly decreased latency to slow wave sleep ($P < 0.05$) and increased duration of stage II slow wave sleep in dogs ($P < 0.01$) in a dose-dependent manner (Winrow *et al.*, 2012b). In rats, MK-6096 also decreased latency to slow wave non-REM sleep and REM sleep ($P < 0.01$) and increased the duration of REM sleep ($P < 0.001$) at all doses (Winrow *et al.*, 2012b). Results were similar in this study with the MK-6096 analogue, DORA-22. Sleep-promoting effects were not observed in murine orexin receptor knockouts with DORA-22, and MK-6096 had no significant off-target activities against a large battery of other receptors, indicating the high level of selectivity and specificity of these DORAs (Winrow *et al.*, 2012b).

Overview of clinical data

Current treatments

Benzodiazepines and GABA-A receptor modulators are currently the mainstay treatments for insomnia although other newer treatments such as melatonin agonists are available. Antipsychotics and antidepressants have also become a treatment approach for insomnia – despite a paucity of clinical efficacy data and not having labelling for an insomnia indication – as well as over the counter antihistamines (Schutte-Rodin *et al.*, 2008; Wilson *et al.*, 2010).

There is strong evidence from at least one meta-analysis of randomized, controlled trials to support the efficacy of both benzodiazepines and GABA-A receptor modulators for the short-term treatment of insomnia (Wilson *et al.*, 2010). With short-term treatment, these drugs can improve sleep-onset latency, total sleep time, sleep efficiency, sleep quality and depending on the molecule, may prevent early waking according to both subjective and objective measures (Wilson *et al.*, 2010). The relationships of sedative hypnotics' pharmacokinetic properties, such as half-life and concentration achieved, on therapeutic activity have been reported (Lieberman and Neubauer, 2007). Hypnotics with longer half-lives have correspondingly longer durations of activity provided that they persist at a minimally effective concentration (Figure 2). This may be problematic if the drug remains at therapeutic levels beyond the required rest period. Moreover, dose is also a consideration as increased dose can cause the compound to persist for longer depending on its half-life (Figure 2) (Lieberman and Neubauer, 2007). Insomnia is often a chronic condition and use of benzodiazepines and GABA-A receptor modulators for the long-term treatment of insomnia is not generally recommended based on the evaluated evidence (Wilson *et al.*, 2010). However, it should be noted that while some countries have short-term use restrictions on the labels of some GABA-A receptor modulators, other GABA-A receptor modulators can be used in the long term, for example, eszopiclone, which has 6-month data in its indication label (Sunovion Pharmaceuticals Inc, 2012).

Choice of benzodiazepine or GABA-A receptor modulator depends on patient-specific treatment goals. For example, some benzodiazepines and GABA-A receptor modulators are effective in inducing sleep onset, while others result in a longer duration of sleep or later waking (Schutte-Rodin *et al.*, 2008). Other major considerations in the choosing of treatments for insomnia are safety and tolerability, which will be discussed in a later section.

Evidence for the use of antipsychotics and antidepressants in the treatment of insomnia is relatively weak

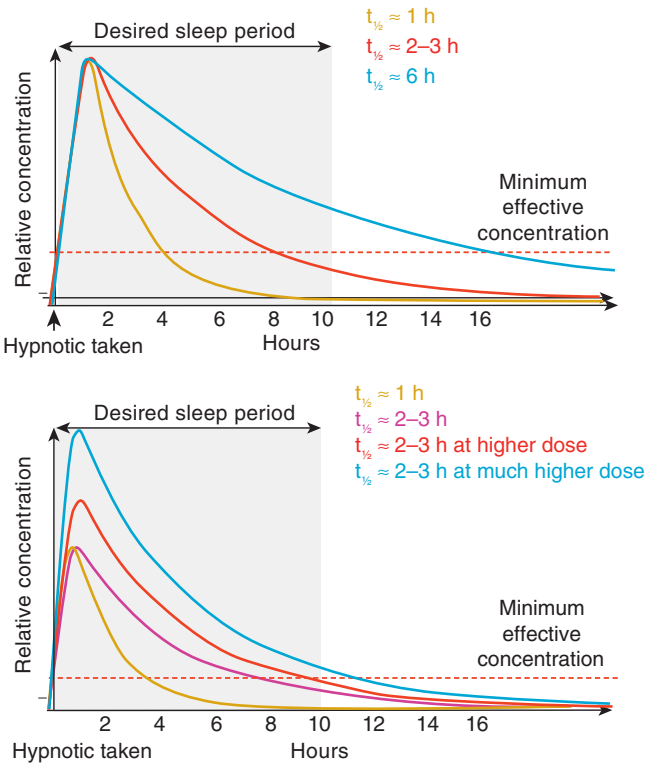

Figure 2

Relationships between the pharmacokinetic profiles of benzodiazepines and GABA-A receptor modulators and their therapeutic activity by half-life (top panel) and concentration (lower panel) (taken from Lieberman and Neubauer, 2007).

compared with that for the use of benzodiazepines and GABA-A receptor modulators (Schutte-Rodin *et al.*, 2008; Wilson *et al.*, 2010). Current guidelines suggest that use of antipsychotics and antidepressants is most appropriate in patients with a psychiatric disorder that is co-morbid with or causative for insomnia (Wilson *et al.*, 2010). There is limited evidence for the efficacy of antihistamines in the treatment of insomnia and their potential for anticholinergic side effects reduces their utility as a long-term treatment (Schutte-Rodin *et al.*, 2008; Wilson *et al.*, 2010). Melatonin agonists were a relatively novel approach at the time of the development of the most recent insomnia treatment guidelines. The mechanism of action of the melatonin agonists relates to the role of endogenous melatonin in inducing drowsiness during circadian regulation of sleep and wake as opposed to the more general hypnotic mechanism historically used to treat insomnia. Early melatonin agonists had relatively short half-lives which may have limited their efficacy in terms of prolonging sleep duration; however, extended-release formulations of these drugs have assisted in overcoming this issue and the evidence base for melatonin agonists in the treatment of insomnia is growing (Wilson *et al.*, 2010). The first melatonin agonist to be approved in the US (in 2005) was ramelteon (Takeda Pharmaceuticals America Inc, 2010). However, ramelteon became approximately 33% less effective at improving latency to persistent sleep in adults in long-term studies as compared with placebo (over 6 months), suggesting that the efficacy of this mechanism may wane over time (Mayer *et al.*, 2009).

Orexin receptor antagonists

There are presently a limited number of published studies that provide clinical data for the DORAs in development.

For SB-649868, Phase I polysomnography data indicated that time to persistent sleep was significantly shorter ($P < 0.001$) and that total sleep time was significantly improved ($P < 0.001$) with SB-649868 30 mg and 60 mg versus placebo in healthy volunteers (Bettica *et al.*, 2012a). In addition, REM sleep duration was significantly increased and REM latency (time from sleep onset to first epoch of REM sleep) decreased with SB-649868 versus placebo. However, duration of wake after sleep onset was not significantly improved with either dose of SB-649868 in this study (Bettica *et al.*, 2012a). In a traffic noise model of situational insomnia in healthy volunteers, treatment with SB-649868 (30 mg) compared with zolpidem (10 mg) resulted in significantly greater increases in total sleep time ($P < 0.001$) as well as significant reductions in time to achieving persistent sleep ($P < 0.001$) (Bettica *et al.*, 2012b). Moreover, compared with placebo, SB-649868 (30 mg) significantly increased REM sleep duration ($P = 0.002$); conversely, zolpidem (10 mg) resulted in a significantly reduced duration of REM sleep ($P = 0.049$) (Bettica *et al.*, 2012b). These results, alongside favourable pharmacokinetic and safety data, led to the Phase II evaluation of SB-649868. In a Phase II randomized, double-blind, placebo-controlled study of 52 patients with primary insomnia, SB-649868 significantly reduced latency to persistent sleep ($P < 0.001$ for all doses), improved duration of wake after sleep onset ($P \leq 0.001$ for 30 mg and 60 mg) and increased total sleep time ($P < 0.001$ for all doses) in a dose-dependent manner (Bettica *et al.*, 2012c). Furthermore, the duration of stage II and REM sleep increased significantly with SB-649868 30 mg and 60 mg ($P < 0.005$). Subjective measures of sleep quantity and quality were also significantly improved in this study (Bettica *et al.*, 2012c).

Almorexant at doses of 100–1000 mg, given in the morning or evening, has been evaluated in healthy volunteers. Following evening administration of the higher almorexant doses, polysomnography indicated that patients had shorter sleep latency, including latency to REM sleep, and had REM sleep of longer duration (Hoever *et al.*, 2012a). When almorexant was administered in the morning, subjects experienced drowsiness and cognitive deficits indicative of sleep induction (Hoever *et al.*, 2012a). In a second study conducted in healthy volunteers, almorexant at doses of ≥200 mg significantly reduced latency to stage 2 sleep ($P \leq 0.03$) and increased sleep efficiency ($P < 0.05$) and total sleep time ($P < 0.05$) compared with baseline measurements (Brisbare-Roch *et al.*, 2007). Zolpidem did not significantly reduce sleep latency in this study. In a double-blind, Phase II randomized study in 161 patients with primary insomnia, almorexant 400 mg significantly improved sleep efficiency versus placebo after the first dose (mean treatment effect 14.4%, $P < 0.001$). In addition, sleep latency was reduced by a mean of 18 min versus placebo ($P = 0.02$) and duration of wake after sleep onset was reduced by a mean of 54 min ($P < 0.001$) (Hoever

et al., 2012b). Almorexant also significantly ($P < 0.05$) improved patient-reported measures of sleep (Hoever *et al.*, 2012b).

In a Phase II randomized, double-blind, 4-week study of 254 patients with primary insomnia, suvorexant 10–80 mg significantly improved sleep efficiency from the first night compared with placebo ($P \leq 0.01$) in a dose-dependent manner, and maintained this treatment difference to the end of the study ($P \leq 0.01$). In addition, all suvorexant doses significantly improved wake after sleep onset at both time points ($P \leq 0.001$). Sleep latency also improved after first treatment with suvorexant 40 and 80 mg (Herring *et al.*, 2012b). General dose-dependent improvements in the total Insomnia Severity Index score were observed compared with placebo for suvorexant 20 mg (–2.0; $P \leq 0.01$), 40 mg (–1.8; $P \leq 0.01$) and 80 mg (–1.6; $P \leq 0.05$). Furthermore, other than subjective refreshed feeling on waking, higher suvorexant doses (40–80 mg) improved patient-reported sleep outcomes on the first night of treatment and at study end (Herring *et al.*, 2012b).

Safety: a rationale for targeting orexin pathway in the treatment of insomnia

Current treatments

Most current medications for insomnia interact with the GABA system, which has multiple functions throughout the brain, resulting in the potential for a broad spectrum of side effects and adverse events. In addition, the pharmacokinetic profiles of classic GABA-mediated medications for insomnia are particularly important as treatments with longer half-lives may result in residual sleepiness and next-day hangover effects such as cognitive impairment, while compounds with short half-lives may not persist within the body for a sufficient period to maintain sleep or reduce instances of wake after sleep onset (Schutte-Rodin *et al.*, 2008; Wilson *et al.*, 2010). Examples of adverse events resulting from the global effects of modulating GABA signalling as well as next-day hangover effects include daytime sedation, confusion, anterograde amnesia and increased falls (Rush *et al.*, 1998; Hindmarch *et al.*, 2006; Roth, 2007; Otmani *et al.*, 2008; Hoque and Chesson Jr, 2009; Roehrs and Roth, 2012). In addition, dependence and tolerance are potential problems with long-term use of benzodiazepines and GABA-A receptor modulators as brain GABA receptor function can change in response to treatment (Wilson *et al.*, 2010).

Orexin receptor antagonists

The main functions of signalling through the orexin system appear to be the promotion of arousal and consolidation of sleep and wakefulness, although orexins have also been implicated preclinically in several areas including reward pathway modulation and changes in animal models of depression. Overall, orexin signalling is not associated with the broad range of roles of the GABA system. It has been posited that the narrower functional remit of the orexin system may indicate that DORAs are a targeted treatment strategy for insomnia with reduced potential for adverse events compared with other commonly targeted treatment pathways (Gotter *et al.*, 2012a,b; Hoever *et al.*, 2012b).

A number of hypothetical safety issues have been investigated during the development of the orexin receptor antagonists based on the mechanism of action. As mentioned earlier, cataplexy – a sudden loss of muscle tone in parts or the whole of the body – occurs in a small proportion of patients with narcolepsy. Even though narcolepsy appears to occur in individuals with near complete and persistent loss of orexin signalling, it has been suggested that attenuating or blocking orexin signalling using pharmacological orexin receptor antagonists may result, not just in the promotion of sleep, but also in the induction of cataplexy. Furthermore, as orexin peptides have a role in maintaining normal sleep architecture, it has been hypothesized that orexin receptor antagonists may dysregulate REM and non-REM sleep stages, resulting in side effects such as sleep fragmentation, hallucinations and sleep paralysis. Additional clinical data are needed to understand these theoretical effects. To date, there have been no reports of cataplexy with almorexant or suvorexant in clinical or preclinical studies (Brisbare-Roch *et al.*, 2007; 2008; Winrow *et al.*, 2011; Hoever *et al.*, 2012a,b; Herring *et al.*, 2012b).

Although SB-649868 is currently listed as undergoing assessment in Phase II trials in the GlaxoSmithKline product pipeline (GlaxoSmithKline, 2012) and data from Phase I and II studies have recently been published (Bettica *et al.*, 2012a,c), an unspecified preclinical toxicity resulted in the development programme for this orexin receptor antagonist being put on hold in 2007 (Scammell and Winrow, 2011). In healthy volunteers, published safety data for SB-649868 showed cognitive impairment versus placebo using the Digit Symbol Substitution Test at peak drug levels. However, when the test was repeated next morning (at drug nadir) this impairment did not persist (Bettica *et al.*, 2012a). In patients with insomnia, the most commonly reported adverse events associated with SB-649868 treatment were headache (in the placebo and SB-649868 10 mg groups), nasopharyngitis (SB-649868 30 mg group) and dry mouth (SB-649868 60 mg group) (Bettica *et al.*, 2012c). In this study, results of cognitive tests performed the morning after treatment were generally comparable between SB-649868 and placebo, although the number of correctly remembered words on the Verbal Learning and Memory Test was significantly lower with active treatment ($P \leq 0.022$) (Bettica *et al.*, 2012c).

Overall, findings have been positive regarding almorexant in published reports. In one recent trial, adverse events associated with almorexant (dizziness, nausea, fatigue, headache and dry mouth) were dose-dependent, generally transient and mild to moderate in severity (Hoever *et al.*, 2012b). Almorexant appears to affect sleep architecture in a dose-dependent manner increasing both non-REM and REM sleep, with higher doses decreasing the time to the onset of REM sleep (shortening the duration of non-REM sleep) and also increasing the duration of REM sleep (Hoever *et al.*, 2012b). In this study of patients with primary insomnia, residual treatment effects of almorexant using subjective measures were not reported except for a small increase in mean reaction time (34.7 ms) for almorexant at the highest dose tested (400 mg). No other notable deficits were reported in the cognitive tests performed on waking (Hoever *et al.*, 2012b).

These initial positive findings in humans regarding lack of next-day, residual effects had been portended in animal studies. Treatment with almorexant did not reduce motor performance or grip strength on waking in rats, whereas zolpidem and ethanol not only reduced motor performance but, when given concomitantly, exacerbated each other's effects (Steiner *et al.*, 2011). Unlike zolpidem, almorexant treatment of rats did not potentiate the next-day sedating effects of alcohol – a finding that has since been reproduced in human volunteers (Hoch *et al.*, 2012a). These results indicate that while alcohol and GABA-A receptor modulators produce hangover effects, almorexant treatment permits full alertness on waking. Furthermore, almorexant co-administration did not engender residual sleepiness the next day. Almorexant administration in rats did not lead to the development of tolerance after five nights of treatment; by contrast, zolpidem tolerance was reported with repeated dosing in this study (Brisbare-Roch *et al.*, 2007; 2008). The half-life of almorexant in humans is almost 40 h (Table 2) and is much longer than other DORAs analysed clinically. Although results from animal models and subjective studies in humans indicate that next-day effects with almorexant were not significant, an exceedingly prolonged half-life may nevertheless lead to hangover effects. Yet, despite promising clinical efficacy and safety results, almorexant development was halted in 2011 due to undisclosed adverse effects in clinical trials.

Suvorexant has been reported to be in late clinical development (Herring *et al.*, 2012a,c). In the earlier Phase II trial by Herring and colleagues discussed above, the most common adverse event associated with suvorexant was somnolence, which showed a dose-related increase in events across treatment groups of 1 (1.6%), 3 (4.9%), 6 (10.2%) and 7 (11.5%) for suvorexant 10, 20, 40 and 80 mg, respectively, compared with 1 (0.4%) for placebo. Other adverse events reported in ≥2% of patients were headache 4.9%, dizziness 4.9%, abnormal dreams 4.9%, upper respiratory and urinary tract infection 3.3% for both. One patient discontinued treatment in the suvorexant arm (compared with three patients in the placebo arm) due to experiencing a mild hypnagogic hallucination. Two patients reported transient sleep paralysis (of 2–10 min duration), two patients reported visual hallucinations and one patient reported excessive daytime sleepiness that lasted for 4 h (Herring *et al.*, 2012b). Anterograde amnesia, a side effect that has been associated with GABA-A receptor modulator use, was not reported, nor were there adverse events indicative of potential for an abuse liability. No consistent pattern suggestive of rebound insomnia or withdrawal effects was observed after 4 weeks of treatment with suvorexant. Notably, no consistent evidence of next-day residual effects on psychomotor performance (assessed by both the Digit Symbol Substitution Test and the Digit Symbol Copying Test) was observed (Herring *et al.*, 2012b).

Current nonclinical evidence suggests that receptor occupancy of approximately 70–80% is required to block the effects of endogenous orexin and promote sleep (data on file). The necessity for a high-level of receptor occupancy means that a DORA with sleep-promoting effects must maintain a relatively high plasma concentration throughout the designated rest period; however, a requirement for >70% receptor occupancy may reduce the potential for next day effects.

Conclusion

The identification of orexin neuropeptides and their involvement in the regulation of sleep/wake states spurred the pharmaceutical development of new targeted treatments for insomnia. Observations in animal models that functional loss of orexinergic activity was associated with increased sleepiness and fragmented wake led to the notion that pharmacological blockade of orexin receptors might be able to address an underlying cause of insomnia. Early preclinical work provided proof of concept for the orexin receptor blockade hypothesis and validated the orexin receptor antagonist mechanism of action in the induction of sleep. Normally, orexinergic diurnal variation occurs such that orexin activity is highest during waking hours and lowest during the normal sleep period. Administration of DORAs during this latter, inactive phase did not lead to robust sleep effects in healthy animals as endogenous orexin levels were at their nadir. By contrast, effects on sleep promotion were seen when DORAs were administered during times of high orexin activity, namely during the wake phase.

Available clinical data regarding the orexin receptor antagonists indicate that these molecules have many of the desired characteristics of an ideal treatment for patients with chronic insomnia, including both onset and maintenance effects without significant tolerability issues or withdrawal effects (Herring *et al.*, 2012b) (Figure 1).

Benzodiazepines and GABA-A receptor modulators improve certain insomnia symptoms but concerns regarding residual/hangover effects, tolerability and withdrawal limit the widespread and long-term use of some of these medicines for treatment of chronic insomnia.

The orexin receptor antagonists described herein, particularly the DORAs, have subtle differences in terms of their effects on arousal and sleep architecture. Some variability in tolerability profiles, presumably due to differences in pharmacokinetics and binding selectivity for the two receptor subtypes, has been reported. However, DORAs have demonstrated efficacy in clinical trials, resulting in improved sleep latency, increased duration of sleep and decreased wake after sleep onset. Of the DORAs in development, suvorexant is the most clinically advanced, having completed Phase III trials. Final Phase III reports are awaited although top line data have been presented in the past year (Herring *et al.*, 2012a,c).

The ability to create animal models and cell lines for screening of novel molecules that block the orexin receptors presents, not only a means of testing promising therapeutics for insomnia, but also the opportunity to use orexinergic compounds in an exploratory manner and to investigate the role of orexin signalling in other putative indications, including, for example, addiction (see elsewhere in this review), depression, pain and migraine prophylaxis.

Acknowledgements

We thank Jane Bryant, PhD from Complete Medical Communications, who provided medical writing support funded by Merck & Co., Inc. and Anthony Gotter, PhD from Merck & Co., Inc. for his helpful comments on the manuscript.

Conflicts of interest

Christopher Winrow and John Renger are full-time employees of Merck & Co., Inc.

References

American Psychiatric Association (2000). Diagnostic and Statistical Manual of Mental Disorders, Fourth edn. Text Revision. American Psychiatric Association: Washington, DC.

Bergman JM, Roecker AJ, Mercer SP, Bednar RA, Reiss DR, Ransom RW *et al.* (2008). Proline bis-amides as potent dual orexin receptor antagonists. Bioorg Med Chem Lett 18: 1425–1430.

Bettica P, Nucci G, Pyke C, Squassante L, Zamuner S, Ratti E *et al.* (2012a). Phase I studies on the safety, tolerability, pharmacokinetics and pharmacodynamics of SB-649868, a novel dual orexin receptor antagonist. J Psychopharmacol 26: 1058–1070.

Bettica P, Squassante L, Groeger JA, Gennery B, Winsky-Sommerer R, Dijk DJ (2012b). Differential effects of a dual orexin receptor antagonist (SB-649868) and zolpidem on sleep initiation and consolidation, SWS, REM sleep, and EEG power spectra in a model of situational insomnia. Neuropsychopharmacology 37: 1224–1233.

Bettica P, Squassante L, Zamuner S, Nucci G, Danker-Hopfe H, Ratti E (2012c). The orexin antagonist SB-649868 promotes and maintains sleep in men with primary insomnia. Sleep 35: 1097–1104.

Beuckmann CT, Sinton CM, Williams SC, Richardson JA, Hammer RE, Sakurai T *et al.* (2004). Expression of a poly-glutamine-ataxin-3 transgene in orexin neurons induces narcolepsy-cataplexy in the rat. J Neurosci 24: 4469–4477.

Brisbare-Roch C, Dingemanse J, Koberstein R, Hoever P, Aissaoui H, Flores S *et al.* (2007). Promotion of sleep by targeting the orexin system in rats, dogs and humans. Nat Med 13: 150–155.

Brisbare-Roch C, Clozel M, Jenck F (2008). Effects of repeated oral administration of the orexin receptor antagonist almorexant in male rats and dogs. Sleep 31: A38–A38.

Chemelli RM, Willie JT, Sinton CM, Elmquist JK, Scammell T, Lee C *et al.* (1999). Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. Cell 98: 437–451.

Coleman PJ, Renger JJ (2010). Orexin receptor antagonists: a review of promising compounds patented since 2006. Expert Opin Ther Pat 20: 307–324.

Coleman PJ, Schreier JD, Cox CD, Breslin MJ, Whitman DB, Bogusky MJ *et al.* (2012). Discovery of [(2R,5R)-5-{[(5-fluoropyridin-2-yl)oxy]methyl}-2-methylpiperidin-1-yl][5-methyl-2 -(pyrimidin-2-yl)phenyl]methanone (MK-6096): a dual orexin receptor antagonist with potent sleep-promoting properties. ChemMedChem 7: 415–424. 337.

Cox CD, Breslin MJ, Whitman DB, Schreier JD, McGaughey GB, Bogusky MJ *et al.* (2010). Discovery of the dual orexin receptor antagonist [(7R)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methy l-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone (MK-4305) for the treatment of insomnia. J Med Chem 53: 5320–5332.

Crocker A, Espana RA, Papadopoulou M, Saper CB, Faraco J, Sakurai T *et al.* (2005). Concomitant loss of dynorphin, NARP, and orexin in narcolepsy. Neurology 65: 1184–1188.

Di Fabio R, Pellacani A, Faedo S, Roth A, Piccoli L, Gerrard P *et al.* (2011). Discovery process and pharmacological characterization of a novel dual orexin 1 and orexin 2 receptor antagonist useful for treatment of sleep disorders. Bioorg Med Chem Lett 21: 5562–5567.

Dugovic C, Shelton JE, Aluisio LE, Fraser IC, Jiang XH, Sutton SW *et al.* (2009). Blockade of orexin-1 receptors attenuates orexin-2 receptor antagonism-induced sleep promotion in the rat. J Pharmacol Exp Ther 330: 142–151.

Faedo S, Perdona E, Antolini M, Di FR, Merlo PE, Corsi M (2012). Functional and binding kinetic studies make a distinction between OX1 and OX2 orexin receptor antagonists. Eur J Pharmacol 692: 1–9.

GlaxoSmithKline (2012). GlaxoSmithKline product pipeline. Available at: http://www.gsk.com/investors/product-pipeline.html (accessed 11/12/2012).

Gotter AL, Roecker AJ, Hargreaves R, Coleman PJ, Winrow CJ, Renger JJ (2012a). Orexin receptors as therapeutic drug targets. Prog Brain Res 198: 163–188.

Gotter AL, Webber AL, Coleman PJ, Renger JJ, Winrow CJ (2012b). International Union of Basic and Clinical Pharmacology. LXXXVI. Orexin receptor function, nomenclature and pharmacology. Pharmacol Rev 64: 389–420.

Gozzi A, Turrini G, Piccoli L, Massagrande M, Amantini D, Antolini M *et al.* (2011). Functional magnetic resonance imaging reveals different neural substrates for the effects of orexin-1 and orexin-2 receptor antagonists. PLoS ONE 6: e16406.

Grady SP, Nishino S, Czeisler CA, Hepner D, Scammell TE (2006). Diurnal variation in CSF orexin-A in healthy male subjects. Sleep 29: 295–297.

Hara J, Beuckmann CT, Nambu T, Willie JT, Chemelli RM, Sinton CM *et al.* (2001). Genetic ablation of orexin neurons in mice results in narcolepsy, hypophagia, and obesity. Neuron 30: 345–354.

Haynes AC, Jackson B, Chapman H, Tadayyon M, Johns A, Porter RA *et al.* (2000). A selective orexin-1 receptor antagonist reduces food consumption in male and female rats. Regul Pept 96: 45–51.

Herring WJ, Connor K, Ivgy-May N, Snavely D, Snyder E, Liu K *et al.* (2012a). Efficacy and safety of suvorexant, a dual orexin receptor antagonist, in patients with primary insomnia: results from two pivotal trials.

Herring WJ, Snyder E, Budd K, Hutzelmann J, Snavely D, Liu K *et al.* (2012b). Orexin receptor antagonism for treatment of insomnia: a randomized clinical trial of suvorexant. Neurology 79: 2265–2274.

Herring WJ, Snyder E, Paradis E, Liu M, Snavely D, Roth T *et al.* (2012c). Long term safety and efficacy of suvorexant in patients with primary insomnia. J Sleep Disord Res 35: A217. abstract 0641.

Hindmarch I, Legangneux E, Stanley N, Emegbo S, Dawson J (2006). A double-blind, placebo-controlled investigation of the residual psychomotor and cognitive effects of zolpidem-MR in healthy elderly volunteers. Br J Clin Pharmacol 62: 538–545.

Hoch M, Hoever P, Alessi F, Marjason J, Dingemanse J (2011a). Pharmacokinetics and tolerability of almorexant in Japanese and Caucasian healthy male subjects. Pharmacology 88: 121–126.

Hoch M, Hoever P, Haschke M, Krahenbuhl S, Dingemanse J (2011b). Food effect and biocomparison of two formulations of the dual orexin receptor antagonist almorexant in healthy male subjects. J Clin Pharmacol 51: 1116–1121.

Hoch M, Hay JL, Hoever P, de Kam ML, Te Beek ET, van Gerven JM *et al*. (2012a). Dual orexin receptor antagonism by almorexant does not potentiate impairing effects of alcohol in humans. Eur Neuropsychopharmacol 23: 107–117.

Hoch M, Hoever P, Alessi F, Theodor R, Dingemanse J (2012b). Pharmacokinetic interactions of almorexant with midazolam and simvastatin, two CYP3A4 model substrates, in healthy male subjects. Eur J Clin Pharmacol 69: 523–532.

Hoch M, Hoever P, Zisowsky J, Priestley A, Fleet D, Dingemanse J (2012c). Absolute oral bioavailability of almorexant, a dual orexin receptor antagonist, in healthy human subjects. Pharmacology 89: 53–57.

Hoever P, de Haas SL, Dorffner G, Chiossi E, van Gerven JM, Dingemanse J (2012a). Orexin receptor antagonism: an ascending multiple-dose study with almorexant. J Psychopharmacol 26: 1071–1080.

Hoever P, Dorffner G, Benes H, Penzel T, Danker-Hopfe H, Barbanoj MJ *et al*. (2012b). Orexin receptor antagonism, a new sleep-enabling paradigm: a proof-of-concept clinical trial. Clin Pharmacol Ther 91: 975–985.

Hoque R, Chesson AL Jr (2009). Zolpidem-induced sleepwalking, sleep related eating disorder, and sleep-driving: fluorine-18-flourodeoxyglucose positron emission tomography analysis, and a literature review of other unexpected clinical effects of zolpidem. J Clin Sleep Med 5: 471–476.

Langmead CJ, Jerman JC, Brough SJ, Scott C, Porter RA, Herdon HJ (2004). Characterisation of the binding of [3H]-SB-674042, a novel nonpeptide antagonist, to the human orexin-1 receptor. Br J Pharmacol 141: 340–346.

de Lecea L, Kilduff TS, Peyron C, Gao XB, Foye PE, Danielson PE *et al*. (1998). The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. Proc Natl Acad Sci U S A 95: 322–327.

Li AH, Nattie E (2010). Antagonism of rat orexin receptors by almorexant attenuates central chemoreception in wakefulness in the active period of the diurnal cycle. J Physiol 588: 2935–2944.

Lieberman JAI, Neubauer DN (2007). Understanding insomnia: diagnosis and management of a common sleep disorder. J Fam Pract 56: 35A–49A.

Lin L, Faraco J, Li R, Kadotani H, Rogers W, Lin XY *et al*. (1999). The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. Cell 98: 365–376.

McAtee LC, Sutton SW, Rudolph DA, Li X, Aluisio LE, Phuong VK *et al*. (2004). Novel substituted 4-phenyl-[1,3]dioxanes: potent and selective orexin receptor 2 (OX(2)R) antagonists. Bioorg Med Chem Lett 14: 4225–4229.

McElhinny CJ Jr, Lewin AH, Mascarella SW, Runyon S, Brieaddy L, Carroll FI (2012). Hydrolytic instability of the important orexin 1 receptor antagonist SB-334867: possible confounding effects on *in vivo* and *in vitro* studies. Bioorg Med Chem Lett 22: 6661–6664.

Malherbe P, Borroni E, Gobbi L, Knust H, Nettekoven M, Pinard E *et al*. (2009). Biochemical and behavioural characterization of EMPA, a novel high-affinity, selective antagonist for the OX(2) receptor. Br J Pharmacol 156: 1326–1341.

Mang GM, Durst T, Burki H, Imobersteg S, Abramowski D, Schuepbach E *et al*. (2012). The dual orexin receptor antagonist almorexant induces sleep and decreases orexin-induced locomotion by blocking orexin 2 receptors. Sleep 35: 1625–1635.

Mayer G, Wang-Weigand S, Roth-Schechter B, Lehmann R, Staner C, Partinen M (2009). Efficacy and safety of 6-month nightly ramelteon administration in adults with chronic primary insomnia. Sleep 32: 351–360.

Mignot E, Lammers GJ, Ripley B, Okun M, Nevsimalova S, Overeem S *et al*. (2002). The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Arch Neurol 59: 1553–1562.

Morgenthaler T, Kramer M, Alessi C, Friedman L, Boehlecke B, Brown T *et al*. (2006). Practice parameters for the psychological and behavioral treatment of insomnia: an update. An american academy of sleep medicine report. Sleep 29: 1415–1419.

Morgenthaler TI, Kapur VK, Brown T, Swick TJ, Alessi C, Aurora RN *et al*. (2007). Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. Sleep 30: 1705–1711.

Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E (2000). Hypocretin (orexin) deficiency in human narcolepsy. Lancet 355: 39–40.

Otmani S, Demazieres A, Staner C, Jacob N, Nir T, Zisapel N *et al*. (2008). Effects of prolonged-release melatonin, zolpidem, and their combination on psychomotor functions, memory recall, and driving skills in healthy middle aged and elderly volunteers. Hum Psychopharmacol 23: 693–705.

Peyron C, Faraco J, Rogers W, Ripley B, Overeem S, Charnay Y *et al*. (2000). A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. Nat Med 6: 991–997.

Porter RA, Chan WN, Coulton S, Johns A, Hadley MS, Widdowson K *et al*. (2001). 1,3-Biarylureas as selective non-peptide antagonists of the orexin-1 receptor. Bioorg Med Chem Lett 11: 1907–1910.

Renger JJ, Kern JT (2011). Preface to the special issue 'Novel pharmaconeurogenetic approaches arising from progress in translational genetics. J Neurogenet 25: 117–119.

Renzulli C, Nash M, Wright M, Thomas S, Zamuner S, Pellegatti M *et al*. (2011). Disposition and metabolism of [14C]SB-649868, an orexin 1 and 2 receptor antagonist, in humans. Drug Metab Dispos 39: 215–227.

Roehrs T, Roth T (2012). Insomnia pharmacotherapy. Neurother 9: 728–738.

Roth T (2007). A physiologic basis for the evolution of pharmacotherapy for insomnia. J Clin Psychiatry 68 (Suppl. 5): 13–18.

Rush CR, Armstrong DL, Ali JA, Pazzaglia PJ (1998). Benzodiazepine-receptor ligands in humans: acute performance-impairing, subject-rated and observer-rated effects. J Clin Psychopharmacol 18: 154–165.

Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H *et al*. (1998). Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell 92: 573–585.

Scammell TE, Winrow CJ (2011). Orexin receptors: pharmacology and therapeutic opportunities. Annu Rev Pharmacol Toxicol 51: 243–266.

Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M (2008). Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med 4: 487–504.

Smart D, Sabido-David C, Brough SJ, Jewitt F, Johns A, Porter RA *et al*. (2001). SB-334867-A: the first selective orexin-1 receptor antagonist. Br J Pharmacol 132: 1179–1182.

Steiner MA, Lecourt H, Strasser DS, Brisbare-Roch C, Jenck F (2011). Differential effects of the dual orexin receptor antagonist almorexant and the GABA(A)-alpha1 receptor modulator zolpidem, alone or combined with ethanol, on motor performance in the rat. Neuropsychopharmacology 36: 848–856.

Sun H, Kennedy WP, Wilbraham D, Lewis N, Calder N, Li X *et al*. (2013). Effects of suvorexant, an orexin receptor antagonist, on sleep parameters as measured by polysomnography in healthy men. Sleep 36: 259–267.

Sunovion Pharmaceuticals Inc (2012). Lunesta product label. Available at: http://www.lunesta.com/PostedApprovedLabeling Text.pdf (accessed 28/2/2013).

Taheri S, Sunter D, Dakin C, Moyes S, Seal L, Gardiner J *et al*. (2000). Diurnal variation in orexin A immunoreactivity and prepro-orexin mRNA in the rat central nervous system 3. Neurosci Lett 279: 109–112.

Takeda Pharmaceuticals America Inc (2010). Rozerem product label. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021782s011lbl.pdf (accessed 28/2/2013)

Thannickal TC, Siegel JM, Nienhuis R, Moore RY (2003). Pattern of hypocretin (orexin) soma and axon loss, and gliosis, in human narcolepsy. Brain Pathol 13: 340–351.

Wilson SJ, Nutt DJ, Alford C, Argyropoulos SV, Baldwin DS, Bateson AN *et al*. (2010). British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. J Psychopharmacol 24: 1577–1601.

Winrow CJ, Gotter AL, Cox CD, Doran SM, Tannenbaum PL, Breslin MJ *et al*. (2011). Promotion of sleep by suvorexant – a novel dual orexin receptor antagonist. J Neurogenet 25: 52–61.

Winrow CJ, Gotter AL, Coleman PJ, Hargreaves R, Renger J (2012a). Recent chronology of orexin pharmacology and its potential as a treatment for primary insomnia. In: Rankovic Z, Bingham M, Nestler EJ, Hargreaves R (eds). Drug Discovery for Psychiatric Disorders. The Royal Society of Chemistry: London, pp. 416–442.

Winrow CJ, Gotter AL, Cox CD, Tannenbaum PL, Garson SL, Doran SM *et al*. (2012b). Pharmacological characterization of MK-6096 – a dual orexin receptor antagonist for insomnia. Neuropharmacology 62: 978–987.

Zeitzer JM, Buckmaster CL, Parker KJ, Hauck CM, Lyons DM, Mignot E (2003). Circadian and homeostatic regulation of hypocretin in a primate model: implications for the consolidation of wakefulness. J Neurosci 23: 3555–3560.