Emerging therapies for sleep disorders

There has been an upsurge in interest in treatments for sleep disorders recently, as new discoveries in the physiology of sleep-related brain neurotransmitter systems have been made. New targets for therapies have been identified in the field of insomnia, and these will be described in this article.

Insomnia affects between 7 and 20% of the adult population, depending on criteria used, and increases in prevalence with age. It significantly impairs quality of life (Alford and Wilson, 2008); sufferers report fatigue, diminished energy and concentration, and memory disturbance. As well as direct treatment costs there are costs related to absenteeism, reduced productivity, accidents, and increased GP visits secondary to the insomnia. Insomnia is a long-term problem, with many patients reporting a duration of more than 20 years (Green et al, 2005). It increases the risk of future disorders, such as anxiety and depression, and is prevalent in psychiatric populations, with up to 90% of depressed patients suffering insomnia (Stewart et al, 2006). It often predates the onset of the psychiatric disorder and if not fully treated is a risk factor for relapse (Dombrovski et al, 2007).

Currently available drugs

Medications currently licensed for insomnia are effective and most are safe in overdose, but despite extensive evidence that insomnia is often enduring and problematic, in the UK and Europe use of hypnotic drugs for more than 3 weeks is restricted. Psychological treatment that includes cognitive behavioural therapy is effective for chronic insomnia (Morin et al, 2006), but is not widely available. In the author's sleep clinic about half of insomnia patients referred for this therapy are unable or unwilling to attend. Some clinicians avoid the issue of short-term use of hypnotics by repeatedly initiating short-term courses. Others resort to long-term prescribing of drugs with unproven efficacy in chronic insomnia, such as tricyclic antidepressants, that have no prescribing restrictions but significant safety issues (Nutt, 2005a).

Most licensed drugs used in insomnia increase the function of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the brain. Both the benzodiazepine and non-benzodiazepine Z-drugs (zolpidem, zopiclone and zaleplon) hypnotics act on the benzodiazepine binding site of the $GABA_A$/benzodiazepine receptor to enhance the effects of GABA. Benzodiazepine tolerance and withdrawal are thought to be the result of adaptive alterations in endogenous GABA function following chronic agonist stimulation of the receptor which leads to profound changes in receptor function, in particular a shift in the direction of enhanced inverse agonist function (Nutt and Malizia, 2001). These are probably the result of altered $GABA_A$/benzodiazepine receptor subunit expression (see below). Such functional receptor adaptations are not produced to the same extent by cyclopyrrolones such as zopiclone (Piot et al, 1990) or imidazopyridines such as zolpidem (Perrault et al, 1992), perhaps because of their different receptor selectivity or differences in the precise molecular mechanisms of their interactions with the receptor (Doble et al, 2004).

This increase in $GABA_A$ transmission has sedative, anticonvulsant and anti-anxiety effects that differ between agents for pharmacodynamic and pharmacokinetic reasons. The shorter acting benzodiazepines, such as temazepam, produce less next day sedation than older drugs, but still have half-lives that extend into the morning. They are also prone to abuse, dependence and withdrawal reactions, which has led to recommendations that they should only be used in the short term (Joint Formulary Committee, 2008). This recommendation is also applied, probably by default, to the Z-drugs, despite limited evidence of adverse effects, tolerance or withdrawal (Nutt, 2005b). However, none of these drugs has good evidence of long-term efficacy, so prolonged use, although common, is not supported by placebo-controlled trial data. In spite of calls for clinical trials of long-term efficacy and safety, there appears not to be the incentive or funding to do these studies as Z-drugs are no longer in patent.

Emerging therapies

After a period in which no new drugs were developed, there has been a revival of interest, in part triggered by the discovery of the involvement in sleep of orexins (also known as hypocretins) in the hypothalamic sleep-regulating centres and of the role of $GABA_A$ receptor subtypes in sleep and anxiety. There is also growing knowledge of the effects of different serotonin receptors on sleep (*Figure 1*).

Development of new drugs is to some extent focussed on improving and refining characteristics such as selectivity or pharmacokinetic properties of GABA-modulating drugs; the other main areas of development have been drugs that affect only subtypes of GABA-benzodiazepine receptors, affect GABA more directly and not via the benzodiazepine site, or which affect other systems, e.g. orexin, serotonin or melatonin neurotransmission (*Figure 2*). Improving the pharmacokinetic characteristics of current drugs has focussed on two areas:

- Prolonging the action of a short-acting drug: zolpidem (half-life 2–3 hours) is helpful for problems with sleep onset but less effective for reducing waking later in the night, whereas controlled-release zolpidem is

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licensed in the USA with the same rapid onset but longer duration of action
- Using different routes of administration to allow rapid absorption and thus development for use after waking in the middle of the night. Several formulations are under investigation, including sublingual and oral spray zolpidem, and inhaled zaleplon.

Improving pharmacodynamic effects

One route to producing new therapies focuses on improving pharmacodynamic effects of currently available compounds, e.g. eszopiclone. The active S-enantiomer of zopiclone, eszopiclone, has been purified and used in its own right as an hypnotic. This appears to give rise to less hangover than the racemic mixture (zopiclone), perhaps because the inactive R-enantiomer has some unwanted actions. Eszopiclone is licensed for 6 months' use in the USA, based on two placebo-controlled trials showing efficacy over 6 and 12 months (Krystal et al, 2003; Roth et al, 2005). Although in practice many patients are treated with hypnotics for many months or longer, these are the first controlled data showing continued efficacy and few problems during withdrawal. This will be very reassuring to patients with chronic primary insomnia and their treating doctors.

Improving selectivity: $GABA_A$ receptor subtypes

The $GABA_A$/benzodiazepine receptor has many subtypes, the most relevant of which are the ones containing either α1, 2, 3 or 5 subunit proteins as benzodiazepine hypnotics, Z-drugs and benzodiazepine anxiolytics act on these subunits. Preclinical studies show that the α1 subtype is highly expressed in the cortex where it mediates sedation and is the primary site of action of zolpidem (McKernan et al, 2000). In contrast the α2 and α3 subtypes are predominantly found in subcortical brain structures that mediate anxiety and sleep and the α5 is particularly localized in the hippocampus where it is involved in memory. Zolpidem was the prototypical α1-receptor subtype selective agonist, and racemic zopiclone shows more activity at α1 receptors than the other subtypes. Unexpectedly eszopiclone is relatively α2/3 selective, which suggests the presumed inactive R-zopiclone enantiomer has some interactions at the $GABA_A$/benzodiazepine receptor to influence the function of the S-enantiomer.

Compounds related to zaleplon, which are more selective for α1 receptors (indiplon) and α2/3 receptors (adipiplon), have been studied for insomnia, but are not currently being taken forward. Indiplon was extensively investigated in phase III studies of insomnia and the immediate release form proved efficacious. However, it is unlikely to be licensed because of regulatory matters and the ending of a proposed marketing partnership. Adipiplon in both immediate release and delayed release forms showed good evidence of efficacy in improving sleep initiation and maintenance and self-reported quality of sleep in phase II studies in insomnia patients. However, when a bilayer tablet combining these two forms was tested in a phase III trial there were puzzling findings with blood concentration levels, suggesting possible problems with the formulation, and trials were suspended. Newer α2/3 selective benzodiazepine receptor agonists are being developed as non-sedating anxiolytic agents (de Haas et al, 2008a,b), but their effects on sleep have not yet been reported.

Other compounds affecting GABA function

It was previously thought that direct-acting $GABA_A$ receptor agonists would not prove useful in treating insomnia, but the agonist gaboxadol has beneficial effects on sleep in insomnia (Lankford et al, 2008). Interestingly this effect on sleep is different to that seen after benzodiazepines in that deep (slow wave) sleep is increased by gaboxadol. Gaboxadol has been studied extensively in primary insomnia, but is no longer being developed for this because it did not promote sleep onset to a sufficient extent even though it had positive actions on sleep continuity.

Another approach in the treatment of insomnia is to decrease the reuptake of released GABA back into neurons or into glial cells by blocking transporters. Tiagabine is a selective GABA reuptake inhibitor that blocks the uptake of GABA back into neurons and some glial cells. It has some beneficial effects on sleep (Walsh et al, 2006); it is now out of patent as an anticonvulsant but may be further developed for sleep problems.

A new compound that appears to act as a partial agonist, allosterically modulating the GABA receptor, is EVT 201. It has shown promising results in phase II

Figure 1. Characteristics of the ideal hypnotic drug.

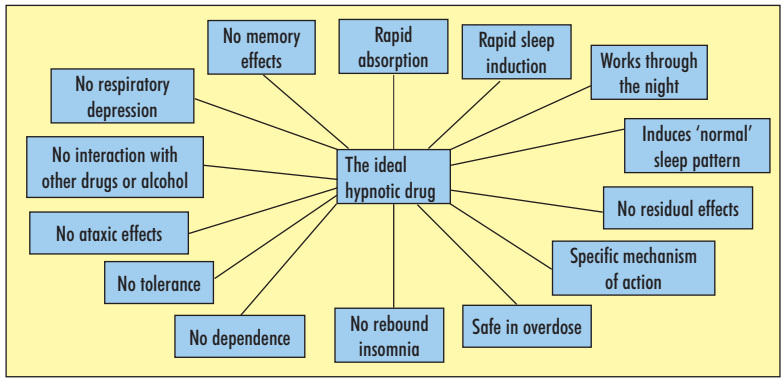
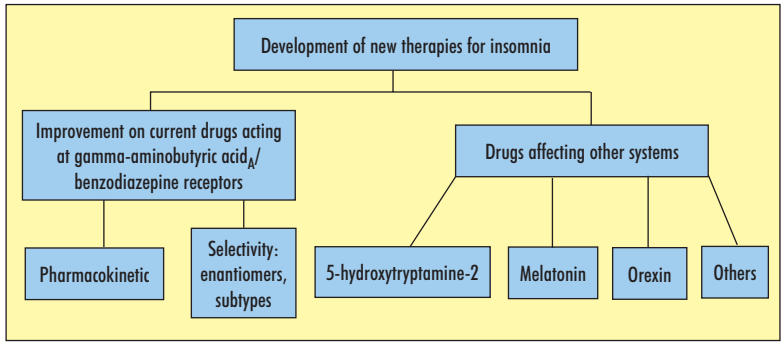


Figure 2. Development of new therapies for insomnia.



studies in a limited number of patients with insomnia, but so far there has been no report of further trials.

Gabapentin and pregabalin were originally thought to be GABA analogues but actually do not directly affect GABA; their action in epilepsy, pain relief and anxiety is probably via their action on calcium channels. However, both confer some benefit in patients with poor sleep related to chronic pain, and also in restless legs syndrome.

Targeting serotonin receptors

Targeting serotonin receptors to improve sleep in insomnia has come to the fore via the problem of sleep disorders in psychiatry, but has a wider significance. Many psychiatric agents act on the serotonin system. The selective serotonin-reuptake inhibitors (SSRIs) often disrupt sleep early in a course of treatment, which seems to be a result of increased 5-hydroxytryptamine (5HT-2) receptor stimulation. In contrast, 5HT-2 antagonists ameliorate the sleep disturbance of depression early in treatment (Hicks et al, 2002), which has led to interest in 5HT-2 antagonists as potential treatments of insomnia. Trazodone has 5HT-2 blocking properties and improved subjective measures of sleep in a study of primary insomnia and objective measures in caffeine-induced insomnia in healthy subjects (Paterson et al, 2007). In insomnia secondary to depression it improves sleep continuity from the first dose, but there are no controlled polysomnography studies in insomnia. However, for many years psychiatrists, especially in the USA, have added trazodone at night to SSRIs when they cause sleep disruption. It has a moderately long half-life and may cause hangover effects in some patients. The S-enantiomer of mirtazapine, another 5HT-2 blocking antidepressant also with H1 receptor antihistamine activity, is being studied in low doses for insomnia, as is doxepin, also at low doses.

The 5HT antagonists are less likely than GABAergic agonists to cause amnesia or ataxia during use, or lead to rebound insomnia on stopping, and their potential for abuse or misuse is minimal. Thus several drugs that are more selective 5HT-2 antagonists are being studied in early clinical trials of insomnia. A selective 5HT-2 antagonist, ritanserin, increased slow wave sleep in healthy volunteers 20 years ago (Idzikowski et al, 1991); in this deep stage of sleep with high amplitude slow (delta) waves in the electroencephalography (EEG), restorative processes in the body take place, e.g. growth hormone is released mainly during slow wave sleep. EEG slow waves are more obvious and of higher amplitude during the first cycle of sleep and gradually diminish during the night, following the same pattern as the sleep drive from the homeostatic process. However, ritanserin had no impact on subjective perception of sleep in healthy volunteers, probably because they slept well at baseline. Studies in poor sleepers were more promising, and several new 5HT-2 antagonists are in development. Eplivaserin is likely to be available first, but three or four more are on the way (*Table 1*). These drugs seem to have more impact on excessive waking during the night than on getting to sleep, so may benefit chronic insomniacs.

One interesting development has been the licensing of agomelatine for depression. It is an effective antidepressant (Kennedy et al, 2008) that combines a 5HT-2 antagonist and melatonin receptor agonist (see below). Both of these properties have the potential to improve sleep disturbance, and in open studies of insomnia sleep continuity was improved early in treatment. Its potential to improve insomnia in depression is the subject of ongoing research.

Orexin receptor antagonists

The discovery that the orexin (also called hypocretin) neurotransmitter system is crucial in sleep regulation came via studies in narcolepsy, where no detectable orexins were present in CSF (Nishino et al, 2000). Orexin neurons are concentrated in a small area of the lateral hypothalamus known to be involved in sleep regulation, and project to many other areas in the brain. Preclinical studies have revealed that orexin neurons fire only during waking, and augment the ascending arousal system as well as stabilizing the sleep–wake switch so that we remain awake. This is directly impaired in narcolepsy and can explain why the sleep and wake pattern in these patients is so fragmented. Since orexins also affect rapid eye movement (REM) sleep, other aspects of narcolepsy such as cataplexy, when REM sleep-type atonia intrudes into wakefulness, may be attributable to the lack of orexin function.

Antagonists to orexin receptors are under investigation in insomnia, because they should lessen waking. One of these agents, almorexant, has shown a sleep-promoting effect in healthy volunteers during the day (Brisbare-Roch et al, 2007) and is in clinical trials in insomnia. Other orexin antagonists are in the pipeline.

Melatonin and melatonin receptor agonists

Melatonin is produced by the pineal gland during darkness, after a trigger from the hypothalamic suprachiasmatic nucleus, which receives input from the eyes. Early studies of melatonin showed that giving exogenous melatonin affected the circadian rhythm of sleeping and waking. In the 1970s and 1980s evidence was found of a drowsiness-inducing effect of melatonin in humans. Its use in resynchronizing circadian rhythms is now established. Although its effectiveness in insomnia has been inconsistent, it is now established that onset of sleep is accelerated by the melatonin agonist ramelteon (licensed in the USA but not yet in Europe). However, in Europe a controlled-release preparation of melatonin, which improves subjective sleep quality and daytime wellbeing in insomniac patients over 55 years of age, has recently been licensed (*Table 1*). One benefit of melatonergic drugs is that there is no withdrawal or rebound syndrome associated with them. Melatonin has been used for many years for sleep difficulties in children, particularly those with learning difficulties, and a government-funded multicentre controlled trial is underway.

Treatment of severe parasomnias

Parasomnias are unusual episodes or behaviours occurring during sleep that disturb the patient or others. Their classification is easiest to understand by looking at the stage of sleep from which they arise. A clinically relevant feature relates to the ability of the sufferer to remember what has happened; in general, parasomnias arising from deep non-REM sleep are not remembered clearly by the patient and those from REM sleep are. For more information about parasomnias see Bornemann et al (2006).

Parasomnias usually present to doctors when they result in injury to the patient or bed partner, or lead to dangerous behaviours, i.e. wandering outside the house while unaware. In the case of nightmares, they present when the distress they engender impacts on daytime functioning; nightmares are best treated with psychological therapies that have been used for some time, including imagery rehearsal and/or exposure techniques (Krakow et al, 1995). Parasomnias of injurious kind (usually night terrors, sleepwalking and REM behaviour disorder) are rare, but require proper assessment as distinguishing the REM from the non-REM behaviours is important when choosing treatment; for this reason patients are usually referred to specialist sleep centres.

Randomized controlled treatment trials are difficult in patients who suffer parasomnia as the episodes are sporadic (although sometimes nightly or even several times a night) and numbers are small. A large case series of all injurious parasomnias was reported in the 1980s and concluded that the benzodiazepine clonazepam was effective, thus clonazepam is most often used in these disorders. However, many patients find a long-acting benzodiazepine causes unacceptable sedative side effects, sometimes high doses are required, and patients need to remain on the drug for very long periods as the parasomnia recurs on cessation of treatment especially if tolerance has occurred and rebound withdrawal is experienced. Treatment may need to be tailored to the type of parasomnia, since different brain mechanisms are involved.

Newer pharmacological approaches have been described in small series. Paroxetine was very effective for night terrors and sleepwalking (Wilson et al, 1997) and, in children, the serotonin precursor 5-HTP given for 3 weeks abolished or markedly reduced episodes of parasomnia in a double-blind trial (Bruni et al, 2004), supporting possible involvement of serotonin in the pathogenesis.

REM behaviour disorder is an area where knowledge is accumulating rapidly. Many commonly-used psychotropic

Table 1. New therapies: stages of development

Drug type	Name	Manufacturer	Stage
$GABA_A$-benzodiazepine receptor modulator	Eszopiclone	GSK	Licensed in US
	Zolpidem extended release (Ambien CR)	Sanofi-Aventis	Licensed in US
	Zolpidem oral spray (Zolpimist)	Nova Del Pharma	Marketing approval in US 2008
	Zolpidem sublingual (Intermezzo)	Transcept	Application for marketing approval submitted
	(Sublinox)	Orexo	Application for marketing approval submitted
	EVT-201	Evotec	Phase II clinical trials
	Zaleplon inhaled AZ-007 Staccato	Alexza	Phase I complete
5HT-2 antagonist	Eplivanserin (SR46349)	Sanofi-Aventis	Application for marketing approval submitted
	Volinanserin (M100907)	Sanofi-Aventis	Phase III clinical trials
	Pruvanserin (LY-422347)	Eli Lilly	Phase II clinical trials
	Pimavanserin ACP-103	ACADIA Pharmaceuticals	Phase II clinical trials
	ITI-722	Intra-Cellular Therapies	Phase II clinical trials
5HT-2 antagonist histamine H1 antagonist	Hypnion (HY10275) (LY-2624803)	Eli Lilly	Phase II clinical trials suspended
5HT-2 antagonist histamine H1 antagonist, a2 adrenergic antagonist	Esmirtazapine ORG-50081	Organon	Phase III clinical trials
Orexin antagonist	Almorexant	Actelion/GSK	Phase III clinical trials
	MK-4305	Merck	Phase II clinical trials
	649868	GSK	Phase II clinical trials
Melatonin	Melatonin controlled release (Circadin)	Lundbeck/Neurim	Licensed in UK for insomnia in patients over 55 years of age
Melatonin receptor agonist	Ramelteon (Rozerem)	Takeda	Licensed in US for sleep-onset insomnia
	VEC-162	Vanda	Phase III clinical trials
Tricyclic antidepressant histamine H1 antagonist	Doxepin (Silenor)	Somaxon	Application for marketing approval submitted

5HT = 5-hydroxytryptamine; $GABA_A$ = gamma-aminobutyric $acid_A$

drugs, notably most antidepressants, tramadol and possibly some beta blockers make REM behaviour disorder worse or trigger the start of REM behaviour disorder (Gagnon et al, 2006). As with non-REM parasomnias, most REM behaviour disorder (usually elderly) patients are given clonazepam with good efficacy. Anecdotal studies and small case series have highlighted the beneficial effects of melatonin (Kunz and Bes, 1999; Boeve et al, 2003) and clonidine (Nash et al, 2003), and there is some evidence that sodium oxybate improves coexisting REM behaviour disorder in narcolepsy with cataplexy, warranting further studies in idiopathic REM behaviour disorder.

Conclusions

New pharmacological therapies are in the pipeline for insomnia. Those in the later stage of development include drugs which improve the pharmacokinetic characteristics or selectivity of current GABA-modulating hypnotic drugs or where long-term efficacy has been established, and those that use blockade of serotonin receptors or orexin receptors, or stimulation of melatonin receptors, to improve sleep. Some or all of these innovations will be introduced in the near future. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Current insomnia medication is generally safe and effective but none is ideal in pharmacodynamic and pharmacokinetic effects and none is recommended to be prescribed for more than short-term use.
- New therapies involve improving drugs acting at the gamma-aminobutyric acid$_A$/benzodiazepine receptor, and development of those acting on serotononergic, orexinergic and melatonergic systems.
- New drugs affecting serotonin and melatonin receptors are either already available or will be available soon. These have the advantage of not giving rise to tolerance and dependence and may not give rise to rebound insomnia.
- Advantages of new drugs will only be apparent when comparative studies are done.
- Treatment of parasomnias may require different approaches depending on whether they arise from non-rapid eye movement (REM) or REM sleep.