WAKING UP TO NOVEL DISCOVERIES IN SLEEP MEDICINE – EMERGING TREATMENTS FOR INSOMNIA

CASE SCENARIO

At a multidisciplinary professional development event, a local GP, Dr Slotz, tells you that prescribing for patients with insomnia places her in a dilemma, as she understands the risks associated with benzodiazepine and non-benzodiazepine hypnotic use. She was wondering about any new medicines on the horizon to help aid sleep.

Introduction and background

Insomnia is one of the most common sleep disorders worldwide, and is clinically defined according to diagnostic criteria as difficulty in falling asleep, maintaining sleep or waking up too early despite adequate opportunity to sleep, leading to next day functional impairments.[1,2]

In Australia, acute insomnia (symptoms ≥3 days a week but less than 3 months) affects about 30–60% of adults at any given time, with about 10–15% reporting chronic insomnia (symptoms ≥3 months).[3,4] It is proposed that acute precipitants (e.g. trauma, work or financial stress) create a hyperarousal response similar to but at a lower level than the fight or flight stress response. Maladaptive behaviours then develop and, through psychological conditioning, cement the hyperarousal pattern, transitioning the condition from acute to chronic.[3]

The state of being 'asleep' or in a state of 'arousal' in the human body is driven by various mechanisms, including[5–7]:

- physiological activity de-escalation in response to energy levels
- signals from the circadian system
- emotional regulation
- behavioural patterns cemented within socio-cultural norms of work and study or social requirements.

Insomnia treatment

Australian guidelines, consistent with current global guidelines, recommend that cognitive behavioural therapy for insomnia (CBTi) needs to be the first-line approach for the management of insomnia. CBTi creates sustained improvements by addressing the underlying psychological and behavioural causes of insomnia, and help patients re-establish a positive association between bed and sleep, rather than an automatic association between bed and being awake.[8,9] To find out more about CBTi, see the 'Beyond sleep hygiene' CPD article in the September 2024 issue of *Australian Pharmacist*. »

Complete your CPD online at **www.psa.org.au/APcpd** and for the full references scan the QR code

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LEARNING OBJECTIVES

After reading this article, pharmacists should be able to:

- Discuss the physiology of sleep
- Describe current treatment options for insomnia
- Discuss novel and emerging treatments for insomnia.

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Pharmacological treatments for insomnia may sometimes be considered where benefits exceed possible harms. Examples may include cases where the patient is experiencing significant distress or impairment by lack of sleep during acute insomnia, and for supporting patients who do not achieve full symptom remission with CBTi.[10,11]

However, most pharmacological treatments are recommended only for short-term use, and should be provided alongside non-pharmacological management options for insomnia.[10,12]

The physiology of sleep

While complex, it is important to understand the physiological basis of sleep. It has been found that there may be distinct regions and neuronal tracts in the brain that drive wakefulness or sleep.[5]

The propagation and maintenance of wakefulness in the brain

The medullary area in the brain receives many sensory inputs such as light increase at sunrise, clock time and alarms. These signals are then transmitted through a network referred to as the reticular activating system (RAS), which extends from the medullary to the hypothalamic area. It is proposed that glutamatergic firing in the RAS actions wakefulness signals after receipt of the above sensory inputs.[5,13,14] The RAS then sends signals to the basal forebrain, hypothalamus and thalamus.

The hypothalamus houses neurons that produce neuropeptides called orexin A and B, which were discovered in 1998, and represent one of the most exciting discoveries in sleep medicine.[5,13–15] Orexin-producing neurons help us stay awake and alert, especially when we really need to focus, which is critical for survival.[5,14] These neurons reach out to many brain areas that use other wakefulness messengers such as acetylcholine, dopamine, histamine, serotonin and noradrenaline. These areas 'talk back' to the hypothalamus, to further boost wakefulness signals.[5] Similarly, the thalamus is an important region that also serves to relay wakefulness signals from the RAS.[5]

The basal forebrain has a key role relaying signals from the RAS, stimulating cortical activity which allows for decision making and functioning while awake.[5] Neurotransmitters in the basal forebrain include both glutamate and gamma-aminobutyric acid (GABA).[5]

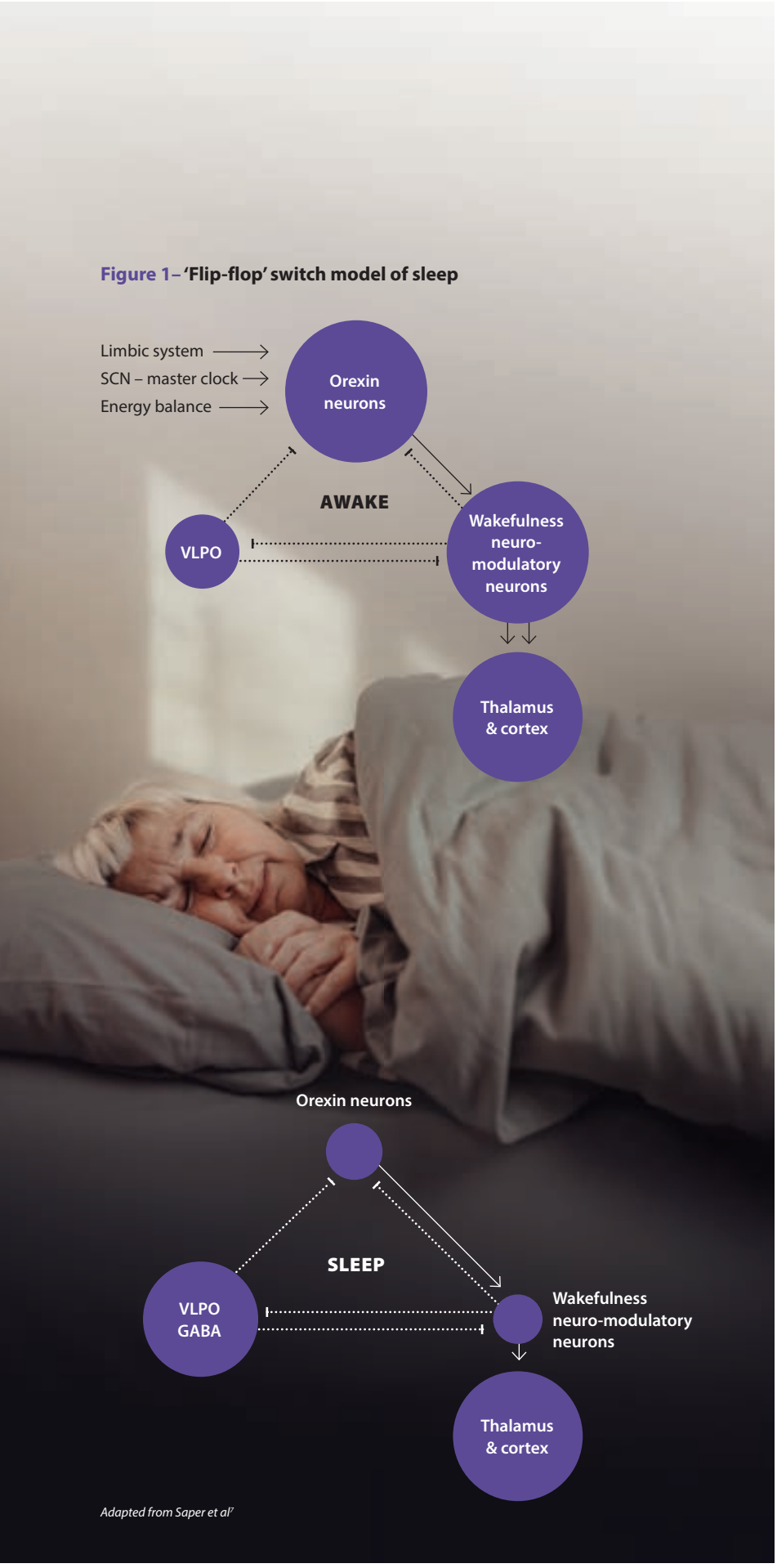
Sleep onset and maintenance

The ventrolateral pre-optic (VLPO) area in the hypothalamus has a dense network of neurons such as GABA, galanin and others which can inhibit activity in brain regions involved in wakefulness and thus promote sleep. The 'quietening down' effect of the VLPO is switched on by increased melatonin levels (triggered by dimmer lighting in the evening) and other sleep-promoting messengers like prostaglandins and adenosine.[5,14]

Overall, selective glutamatergic and GABAergic firing determines the state of being awake or asleep.[14] This reciprocal circuitry between brain arousal and sleep centres was thought to maintain a 'flip-flop' switch as outlined in Figure 1 (i.e. either one is in a state of sleep or is awake).

However, it is now understood, particularly from animal studies, that there may be local brain areas in a sleep/wake state different to the rest of the brain.[16,17]

Figure 1– 'Flip-flop' switch model of sleep



Adapted from Saper et al[7]

Existing pharmacotherapies for insomnia

The most common class of sedatives in practice includes benzodiazepines and non-benzodiazepine hypnotics, which have dominated insomnia treatment over the last 5 decades. These medicines potentiate the GABAergic inhibition at $GABA_A$ receptors within the VLPO to induce sleep.[18] While effective at treating insomnia symptoms, their use is limited by serious adverse effects, including anterograde amnesia, hangover sedation, dependence, tolerance, and risk of falls and fractures. This especially limits use long-term and in older patients.[18–20] Benzodiazepines mainly increase the lighter stages (e.g. phase N2) in the sleep cycle, despite increasing total sleep time and reducing latency to fall asleep.[21]

Non-benzodiazepine hypnotics, such as zolpidem and zopiclone were later marketed and work on the same receptor sites as conventional benzodiazepines, despite their non-benzodiazepine structure.[18] These medicines, considered to have specificity for certain $GABA_A$ receptor sub-types (e.g. zolpidem is specific for alpha-1 $GABA_A$ receptor sub-types) and a lower addiction potential, nonetheless have an adverse effect profile similar to the classic benzodiazepines. Zolpidem has been implicated to have a range of unusual adverse effects, including parasomnias, amnesia and hallucinations, and has generated much publicity.[20]

Melatonin was developed for therapeutic use in insomnia. However, studies have been disappointing and have not shown efficacy in managing insomnia symptoms except for small scale effects in older adults (>55 years) and in children with sleep disturbances linked with neurodevelopmental disorders.[22–24]

A range of antidepressants and antipsychotics have often been used off-label as they can antagonise monoaminergic neuromodulators that »

potentiate wakefulness, but evidence for their use in treating insomnia is not robust.[25] Their impact on a range of receptors also makes users of these medicines more prone to adverse effects.[25] Many antidepressants used 'off-label' for sleep, such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) and selective noradrenaline reuptake inhibitors (SNRIs) also decrease rapid eye movement (REM) sleep (important for memory storage and consolidation).[26] In addition, SSRIs and SNRIs tend to activate the arousal system and may contribute to sleep fragmentation.

Similarly, sedating antihistamines commonly sought from pharmacies, are only effective short term, as tolerance to their sedative effects develop quite quickly. Direct evidence of their efficacy in insomnia in clinical trials is also scarce.[27]

They can also block other monoaminergic receptors in the brain, hence requiring the need for caution in their use due to a broad range of adverse effects.[27]

Novel and emerging treatments for insomnia

Given cortical hyperarousal is one of the pathophysiological causes of insomnia,[3] the discovery of orexin and its potent role in the maintenance of wakefulness has fuelled drug development in this area.

Dual orexin receptor antagonists

Orexin A and orexin B are two neuropeptides derived from the same precursor and act on orexin 1 (OX1) and orexin 2 (OX2) receptors (orexin A binds equally to OX1 and OX2 receptors, while orexin B has higher selectivity for OX2 receptors).[28] The properties of these medicines are highlighted in Table 1.

Another dual orexin receptor antagonist (DORA), vornorexant*, is under development and currently undergoing clinical trials.[28]

Daridorexant* is available overseas for sleep onset and sleep maintenance insomnia, but is not currently available in Australia.[28]

Table 1– Key clinical information on dual receptor orexin antagonists

	Lemborexant (*Dayvigo*)	Suvorexant (*Belsomra*)
Receptor targets	Mainly OX2 and OX1 to a lesser extent	OX1 and OX2
Clinical indication	Sleep onset and sleep maintenance insomnia	Sleep onset and sleep maintenance insomnia
Onset of action (minutes)	30	30
Volume of distribution (litres)	1,970	49
Enzymes for metabolism	CYP3A/CYP2B6	CYP3A/CYP2C19
Metabolites (Yes/No)	Yes, M4/M9/M10	No
Half-life $t_{1/2}$ (hours)	17–19	12
Duration of action (hours)	7	7
Before/after food	Best on an empty stomach	Best on an empty stomach
Recommended treatment duration	Tested in clinical trials for 12 months, but shortest duration required is best[29]	Reassess need for treatment continuation after 3 months
Breastfeeding and pregnancy use	No data	No data
Use in hepatic/renal impairment	No data. Avoid use in severe hepatic impairment (lower dose in moderate impairment)	No data. Avoid use in severe hepatic impairment
Key counselling point	Ensure opportunity to sleep for 7 hours when taking this medicine	Ensure opportunity to sleep for 7 hours when taking this medicine

Reference: *Rossi[30]; Kim et al[28]*

DORAs are believed to lead to lower risk of cognitive and functional impairment when compared to GABA modulators.[28] Results from human and animal studies also highlight that DORAs enable easier arousability from sleep.[31–33] Hangover sedation also appears less likely compared to some benzodiazepines, especially for suvorexant.[28]

Real-world post-marketing data from spontaneous drug reporting in Japan indicates that DORAs have a more favourable safety profile and lower incidence of adverse events, particularly for functional impairment leading to accidents or injuries,[34] and appear less likely to lead to dependence.[35,36]

Compared to medicines such as benzodiazepines, DORAs appear to minimally impact natural sleep architecture, mainly only increasing REM sleep periods.[37] DORAs are also being tested across a range of trials for their role in improving dementia outcomes, possibly through sleep related improvements.[38]

DORAs are contraindicated in narcolepsy (as this condition stems from orexin deficiency). In addition, they are associated with adverse effects such as headaches, sleepiness, dizziness and fatigue. Rarely, abnormal dreams, sleep paralysis, hallucinations during sleep or possible suicidal ideation may occur.[39] Combining DORAs with alcohol or other sedatives can increase the risk of adverse effects and should be avoided.[10]

Comparative trials directly comparing the impact of DORAs with benzodiazepines and other sedatives are relatively lacking, and the effect of DORAs on overall sleep parameters, such as total sleep time or hastening sleep onset, may be lower than that of benzodiazepines.[39] However, they appear to have a more favourable safety profile.

In summary, further research and clinical experience in Australia is needed before DORAs are routinely recommended for use in insomnia.[10]

Single orexin receptor antagonists

Besides DORAs, research is looking at developing single orexin receptor antagonists (SORAs). OX1 receptor binding to orexin signals high potency awake states and suppression of restorative deep sleep. OX1 receptors are also associated with reward-seeking behaviour.

OX2 binding of orexin results in specific suppression of REM sleep and seems critical for wake-promoting effects of orexin.[28] Hence, OX2 selective single orexin receptor antagonists (2-SORAs) are being tested (seltorexant*, in phase III clinical trials) for more tailored treatment of insomnia.[28] »

$GABA_A$ receptor positive allosteric modulators

To overcome some of the issues associated with classic benzodiazepines, newer $GABA_A$ receptor positive allosteric modulators such as lorediplon* and EVT-201* (partial allosteric modulator at $GABA_A$) are under investigation.[28,40]

Other medicines such as dimdazenil* (partial positive allosteric modulator at $GABA_A$ specific to alpha-1 and alpha-5 $GABA_A$ receptor subtypes)[41] and zuranolone* (positive allosteric modulator for $GABA_A$) have also been tested, with positive outcomes in trials. Zuranolone* is marketed overseas specifically for postnatal depression, but clinical trials for its use in insomnia are ongoing.[40]

Synthetic melatonin receptor agonists

Synthetic melatonin receptor agonists target melatonin 1 and 2 receptors (MT1 and MT2) and show some promise of clinical benefit in insomnia symptoms with reasonable tolerability and safety.[42] This class of medicines include[28,30,42,43]:

- Ramelteon* (MT1 specific) – available in other countries, such as the US, for treatment of insomnia. Studies demonstrate that the overall effect on insomnia outcomes is small, though better than that of melatonin itself.
- Tasimelteon* (MT1 and MT2 activity) – available in other countries, such as the US, for treatment of sleep-wake disorders linked to circadian rhythms.
- Agomelatine (MT1 and MT2 agonist and serotonin $5HT2_c$ receptor antagonist) – currently indicated for major depression and generalised anxiety disorder in Australia.

Other medicines

Several 5HT2A antagonists have been trialled, such as eplivanserin*, which demonstrated positive insomnia outcomes, but did not meet the regulatory benefits versus risks criteria when proposed for registration in the US.[44]

There are some trials being conducted with nociceptin/orphanin FQ Receptor (NOP) agonists (e.g. sunobinop*, a partial agonist of NOP). Animal and some minimal human studies indicate that these medicines can increase non-REM sleep and reduce REM sleep.[45]

**Not approved in Australia*

Knowledge to practice

Pharmacists are often asked about new medicines as they become available. Remaining up to date with novel and emerging treatments in sleep health, while reinforcing CBTi as the recommended 'first-line' treatment for insomnia, can ensure pharmacists provide the most current advice in this area.

Conclusion

The field of sleep research and drug discovery is rapidly expanding, with a range of medicines working on various elements of the sleep-wake circuitry in the brain now available. Currently, the most promising emerging categories of sedatives with comparatively safer profiles compared to benzodiazepines are the orexin receptor antagonists and synthetic melatonin receptor agonists. However, research and clinical development is ongoing for many of these novel and emerging treatments.

CASE SCENARIO CONTINUED

You advise Dr Slotz that orexin receptor antagonists are showing promise. Although suvorexant and lemborexant are available in Australia, you advise that research into this medicine class is ongoing and currently there is limited clinical experience with their use in Australia.

When pharmacological treatment is indicated, you discuss taking into consideration the specific insomnia symptoms of patients and individual characteristics in order to specifically tailor their pharmacotherapy.

You also talk about other novel and emerging treatments and highlight that research to develop new treatments for insomnia is rapidly evolving. Finally, you emphasise that CBTi is well established as a first-line treatment for insomnia, with an increasing trend of health professionals training to deliver CBTi in primary care. »

UP TO
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KEY POINTS

- Use of traditional pharmacological treatments for insomnia is often constrained by various factors, such as a wide range of adverse effects, low efficacy or rapid tolerance to sedative effects.
- The field of sleep research and drug discovery is rapidly expanding, with new medicines under clinical development or becoming available in this space.
- Some novel and emerging treatments show promise in offering clinical benefit with a more favourable adverse-effect profile when compared to traditional pharmacological treatments. However, further research is needed in this area.
- Cognitive behavioural therapy for insomnia, a non-pharmacological treatment, remains the recommended first-line treatment for insomnia in Australia. AP

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ASSESSMENT QUESTIONS

Each question has only one correct answer.

1 Which ONE of the following options is *CORRECT* regarding the physiology of sleep?

A Activity in the ventrolateral pre-optic area propagates and amplifies wakefulness signals in the brain.

B The reticular activating system is a neuronal network involved in the transmission of wakefulness signals in the brain.

C Orexin A and B are primarily produced and housed in the thalamus.

D All areas of the brain are in the same sleep/wake state at the same time.

2 Which ONE of the following options is *CORRECT* regarding current pharmacological treatment options for insomnia?

A Zolpidem has been associated with adverse effects such as hallucinations and parasomnias.

B Melatonin has shown consistent efficacy for younger adults experiencing insomnia symptoms.

C Non-benzodiazepine hypnotics work on different receptors to benzodiazepines, but have a similar structure.

D Benzodiazepines promote glutaminergic transmission in the ventrolateral pre-optic area.

3 Which ONE of the following options is *CORRECT* regarding dual orexin receptor antagonists?

A Daridorexant, lemborexant and suvorexant are available in Australia for treatment of insomnia.

B The duration of action for dual orexin receptor antagonists is 15 hours.

C Dual orexin receptor antagonists are contraindicated in narcolepsy.

D Dual orexin receptor antagonists are more likely to cause hangover sedation when compared to benzodiazepines.

4 Which ONE of the following options is *CORRECT* regarding novel and emerging treatments for insomnia?

A Seltorexant is a single orexin receptor antagonist, binding to OX1 receptors.

B Zuranolone, marketed overseas for postnatal depression, is being investigated for use in insomnia.

C Ramelteon, tasimelteon and agomelatine are $GABA_A$ receptor modulators which have better receptor selectivity when compared to benzodiazepines, leading to a more favourable safety profile.

D Agomelatine is currently indicated for insomnia in Australia.