Disclaimer

FOR ONE TO ONE MEETINGS (please delete as applicable)

These slides are in response to your medical enquiry. Please be aware that the information presented and discussed in the meeting may contain off-label information

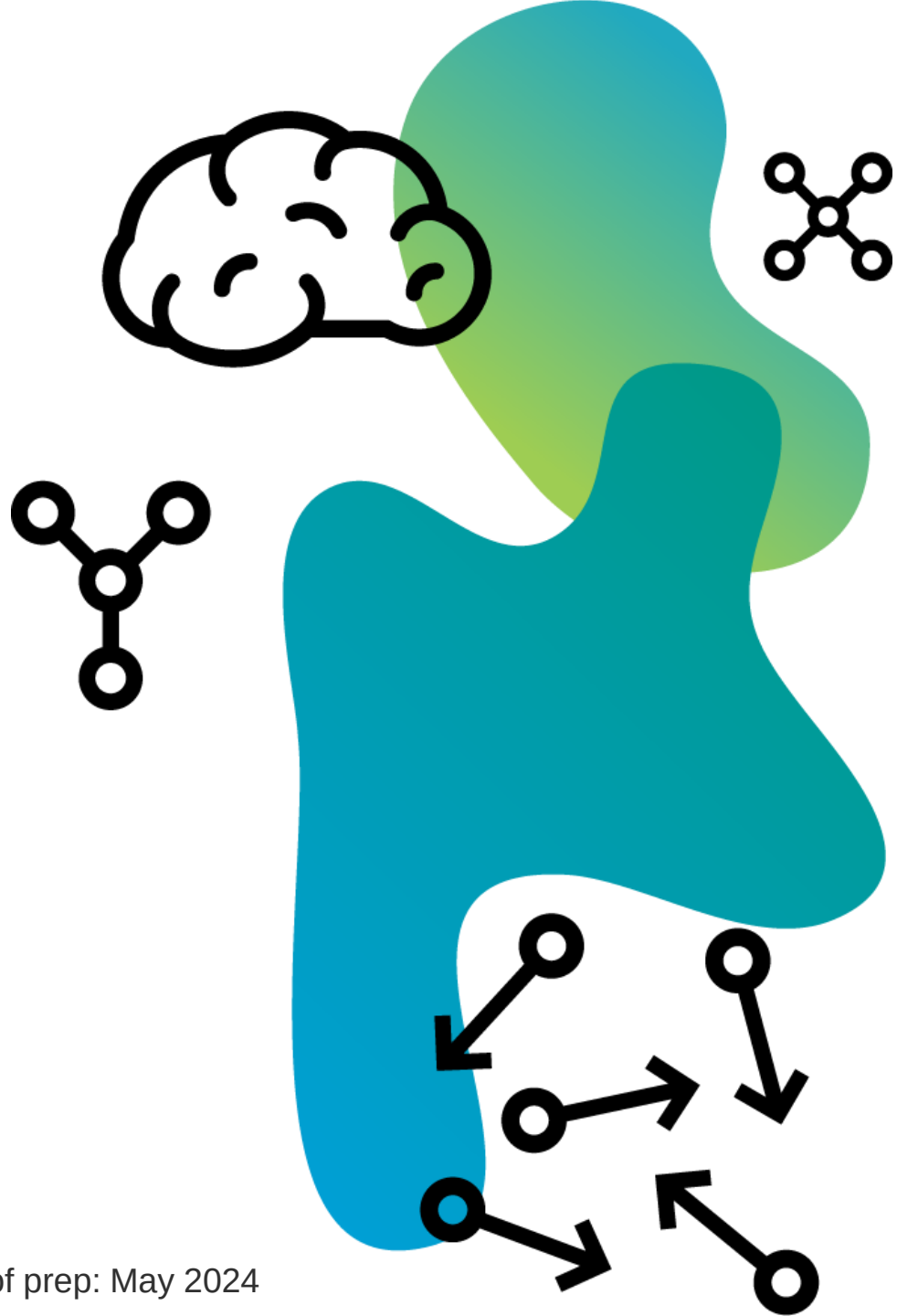
FOR GROUP MEETINGS (please delete as applicable)

This meeting and slides are in response to a medical enquiry received by [INSERT TITLE AND NAME]. By remaining in the meeting, you are confirming that:

- [INSERT TITLE AND NAME] already shared details of the enquiry with you, and you want to know the answer to this enquiry

- You are aware that the information presented and discussed in the meeting may contain off-label information

Introduction to insomnia and its management in the UK



[MSL name]

Medical Science Liaison
Idorsia Pharmaceuticals UK Ltd

MED-UK-DA-2300004

Date of prep: May 2024

Agenda

Introduction to Idorsia

Fundamentals of sleep

- Overview of sleep neurobiology
- Sleep-wake cycle

Introduction to insomnia

- Definition
- Symptoms
- Pathophysiology
- Prevalence and socioeconomic burden

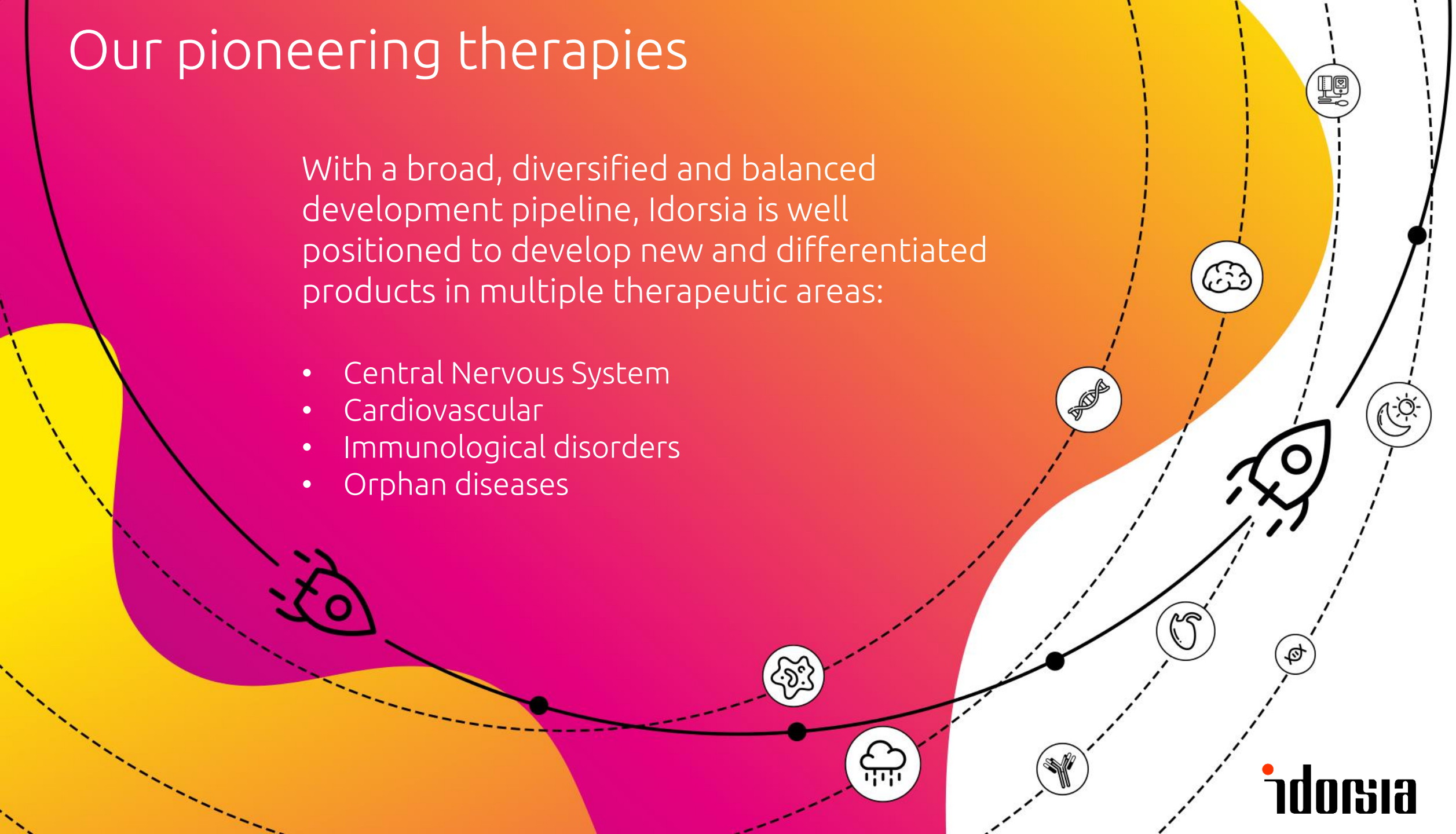
Insomnia management in the UK

- Assessment and diagnosis
- Non-pharmacological treatment options
- Pharmacological treatment options

Our pioneering therapies

With a broad, diversified and balanced development pipeline, Idorsia is well positioned to develop new and differentiated products in multiple therapeutic areas:

- Central Nervous System
- Cardiovascular
- Immunological disorders
- Orphan diseases



Why do we sleep?

Cleaning up the kitchen

From https://www.finedininglovers.com/article/16-rules-kitchen-survival (Copyright-free)

Actively regulated process

Reorganisation of neuronal activity

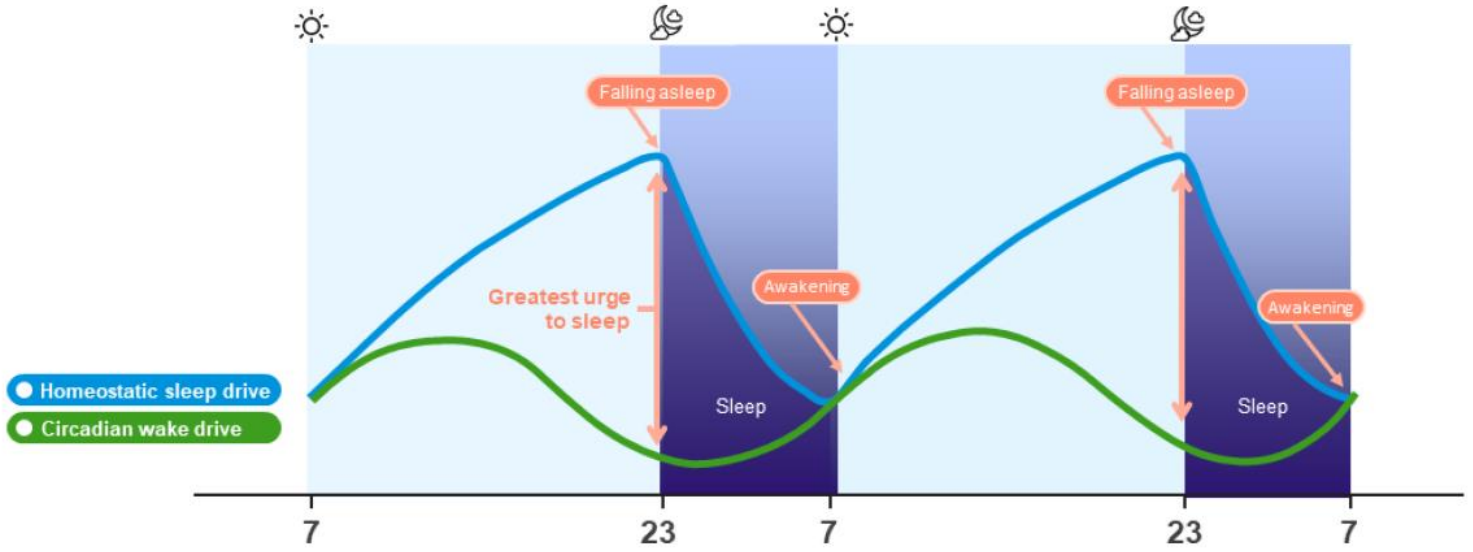
“Of the brain, by the brain, for the brain”

Hobson JA.2005, Nature, 437: 1254-6

Why do we sleep?

Once upon a time…

- Natural and reversible state of increased arousal threshold, reduced responsiveness to external stimuli and relative inactivity, accompanied by a loss of consciousness
- Occurs in regular intervals and is regulated
  - Circadian system imposes and synchronises a ~24h rhythm on the sleep-wake cycle that determines the propensity to sleep or be awake
  - Homeostasis translates into cumulative duration and intensity of sleep after a long period awake



Adapted from Monica and Dijk, 2018. "What makes a good night's sleep?" Available at: What makes a good night's sleep? - The Physiological Society (physoc.org)

Rasch B, Born J. 2013. Physiol Rev, 93(2): 681-766
Besedovsky L, et al. 2019, Physiol Rev 99(3): 1325-80
Monica, Dijk. 2018. Physoc 113: What makes a good night's sleep? - The Physiological Society (physoc.org)

Why do we sleep?

The human pacemaker

- The circadian rhythm pathways are self-sustained, free-running, adapted to the geophysical cycle.
- Zeitgeber determine or readjust the phase/period of the rhythm:
  - Light, exercise, temperature, feeding
- Allows:
  - Metabolic control
  - Sleep
  - Immune response
  - Cardiovascular performance
  - Alertness

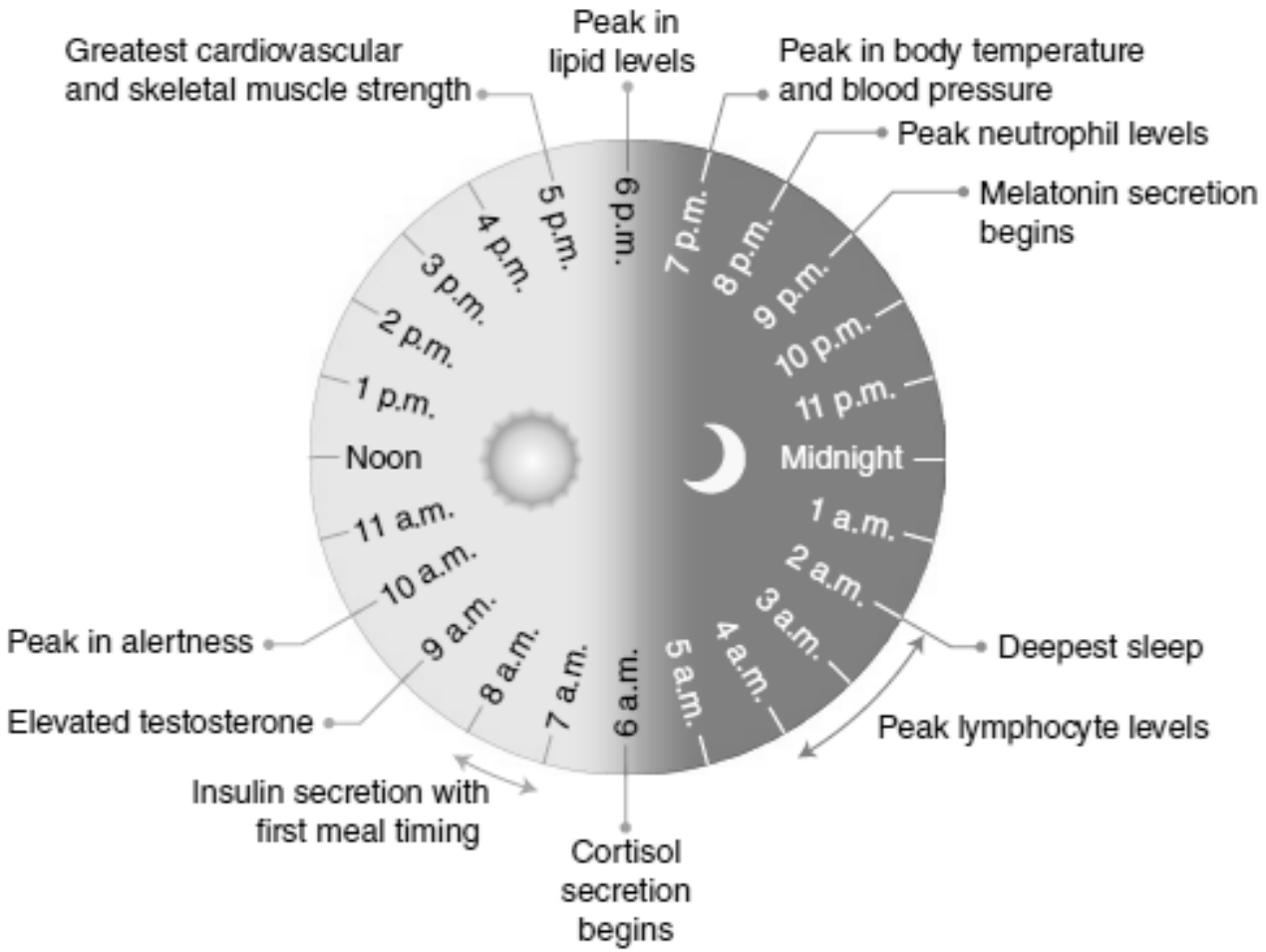


Image adapted from Masri S, Sassone-Corsi P. 2018. Nature Med, 24: 1795-1803
Ruan W, Yuan X, Eltschig HK. 2021. Nature Rev, 20: 287-307

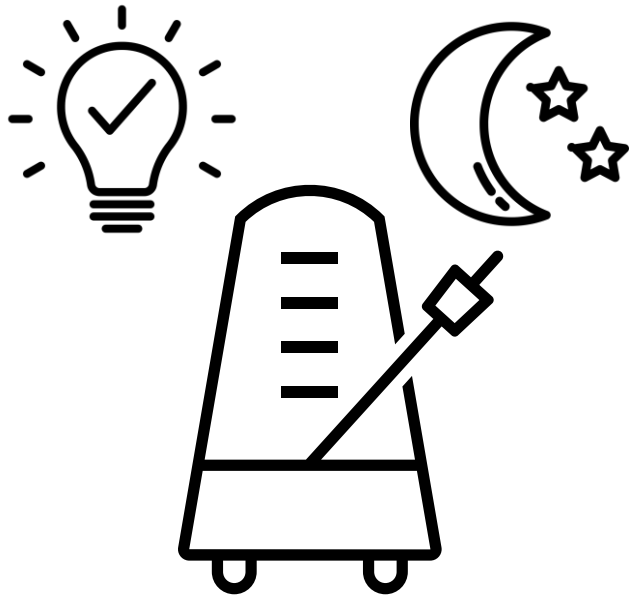
How do we sleep?

The sleep-wake switch

- Sleep-wake cycle is a tightly orchestrated process regulated by both **sleep-promoting** and **wake-promoting** centres in the brain.

A Sleep-promoting system

- GABA
- Melatonin



B Wake-promoting system

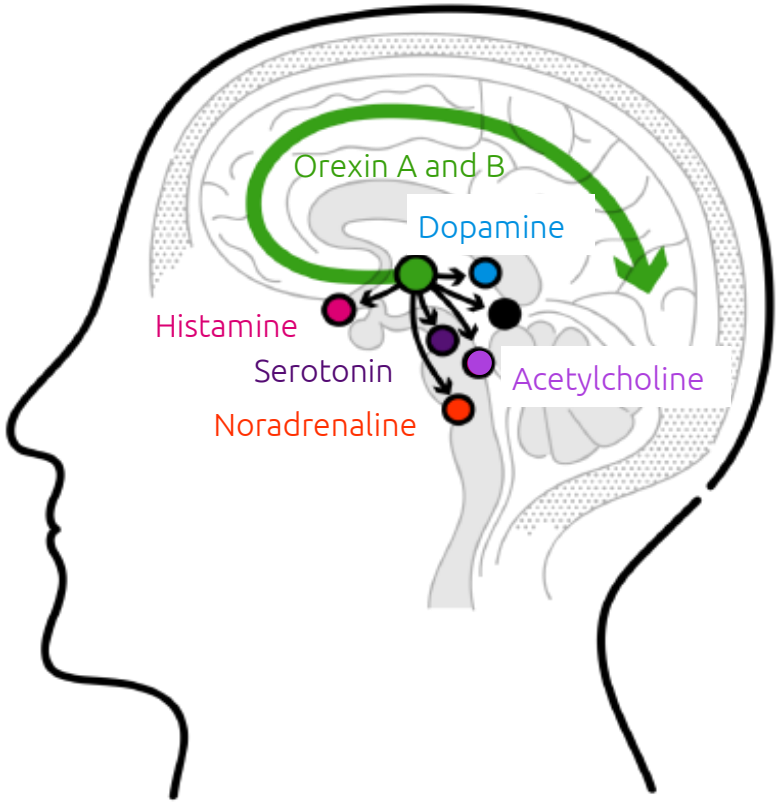
- Histamine
- Noradrenaline
- Serotonin
- Acetylcholine
- Dopamine
- Orexin

Rasch B, Born J. 2013. Physiol Rev, 93(2): 681-766

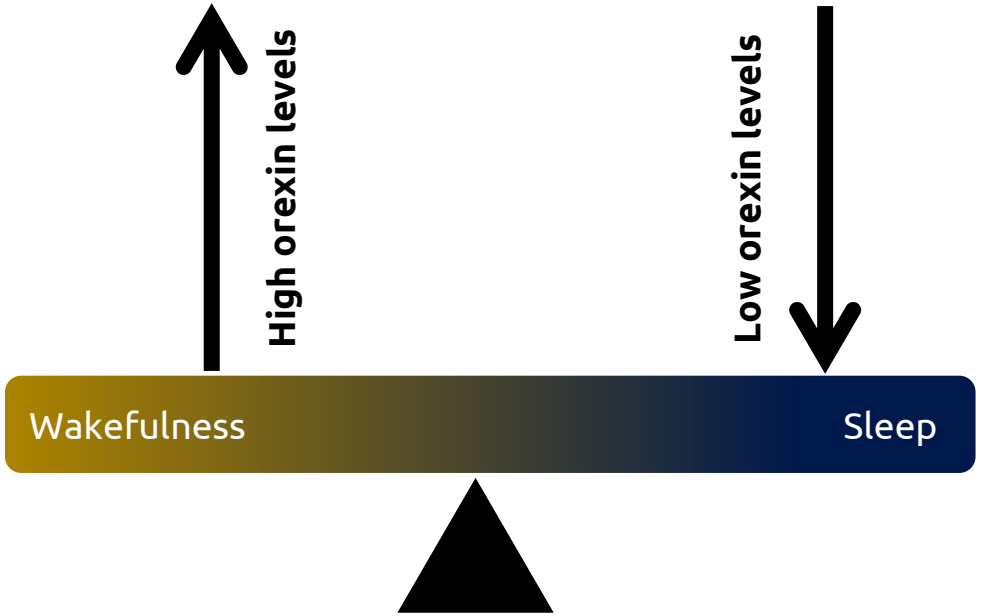
GABA: γ-Aminobutyric acid

What is the orexin system?

Orexin and the regulation of wakefulness

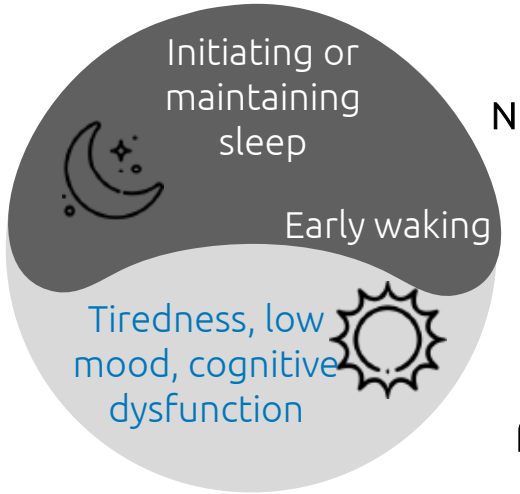


Adapted from Sakurai, 2007. Nature Reviews



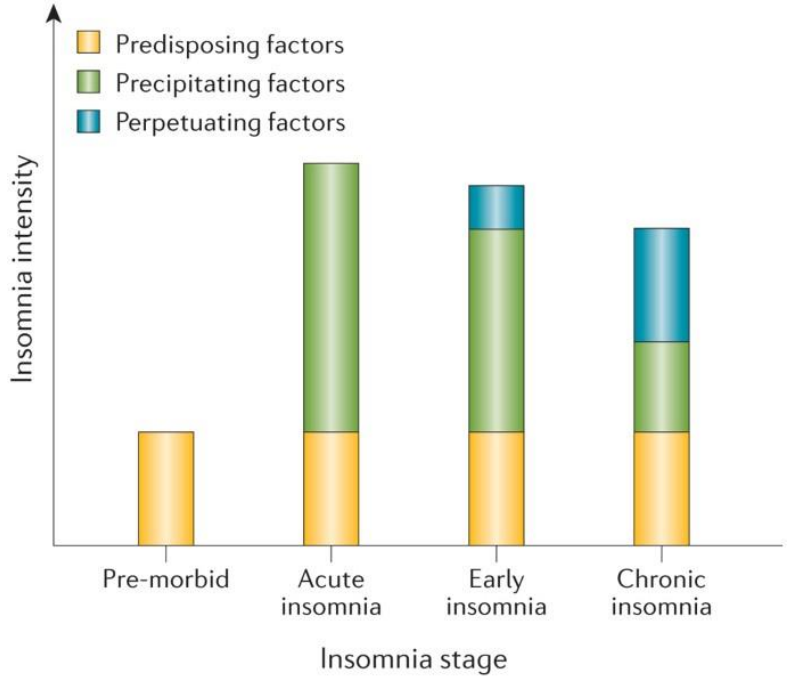
Sakurai, 2007. Nature Reviews
Toor B et al, 2021. Front Neurol Neurosci.
Scammell TE, 2007. Nature Medicine

Pathophysiology of insomnia



Non-restorative sleep

Impaired daytime functioning

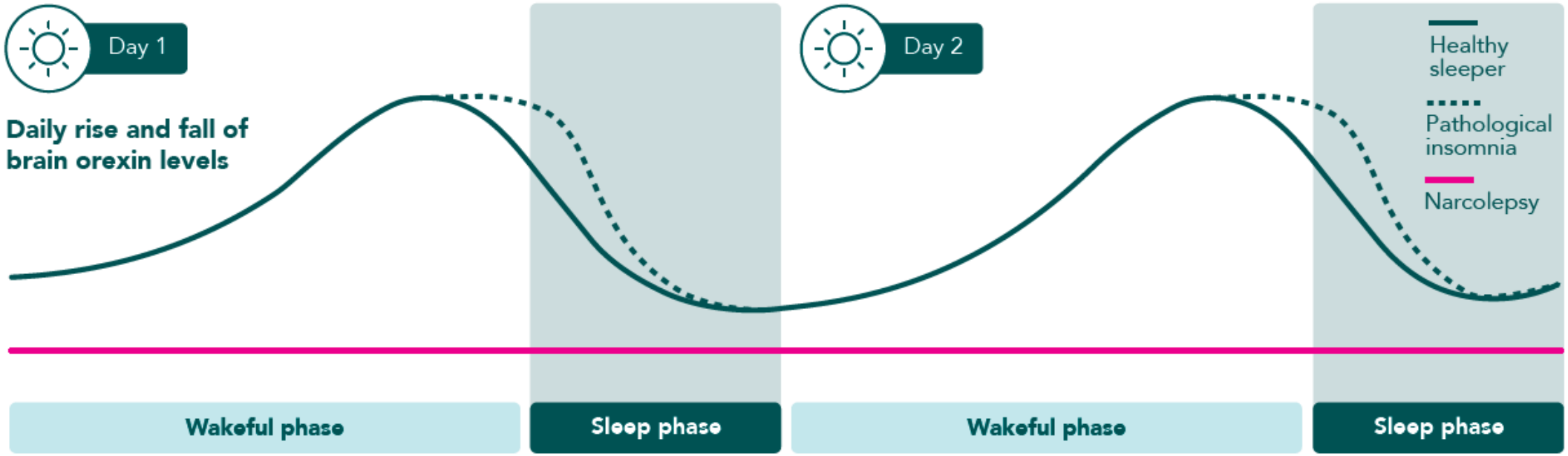


Adapted from Morin et al., 2015, Nature Reviews, Insomnia disorder

- Evidence supports that chronic insomnia is a 24h disorder
- The conscious effort to sleep was also shown to be a contributor for this arousal
- Conditioned arousal associated with psychosocial stress and persistent maladaptive behaviours is a perpetuating factor of insomnia
- Subjective experience of sleep loss, daytime fatigue, and performance impairment
- Neuroendocrine, neuroimmunological, and neuroimaging studies show increased levels of arousal in both night and daytime

Morin CM, et al. 2015 Nature Rev, 1:1-18; Riemann D, et al. 2010. Sleep Med Rev, 14(1):19-31; Feige B, et al. 2008. J Sleep Res , 17:180-90

Impact of hyperarousal



Adapted from Sun, 2021. Front Neurol Neuroscience

It is hypothesized that insomnia may be due to sustained release of orexin which can prolong wakefulness at night[1] (hyperarousal). Hyperarousal at night can lead to disrupted sleep and daytime functioning impairment[2].

1. Sun Y, et al. Front Neurol Neurosci. 2021;45:22-37; **2**. Levenson JC, et al. *Chest*. 2015;147:1179–1192

Roles of sleep and consequences of lacking sleep[1-7]

Physiologic restoration

Energy conservation

Clearance of metabolic waste

Macromolecule synthesis

Modulation of inflammation markers

Memory consolidation

Consequences of lack of sleep[8]

- Short periods of sleep loss at the time of vaccination reduce the vaccine's effectiveness
- Increased obesity, reduced levels of leptin and increased levels of ghrelin. This results in increased appetite.
- Diabetes and impaired glucose tolerance in a dose-related manner
- Increased hypertension and cardiovascular risk increases 45% in individuals who chronically sleep 5h per night or less

1. Purves D, et al, eds. *Neuroscience*. 6th ed: Sinauer Associates; 2018; 2. Kryger MH, et al, eds. *Principles and Practice of Sleep Medicine*. 6th ed. Elsevier; 2017; 3. Peever J, et al. *Curr Biol*. 2017;27(22):R1237-R1248; 4. Schwartz JR, et al *Curr Neuropharmacol*. 2008;6(4):367-378; 5. Landolt HP, et al, eds. *Sleep-Wake Neurobiology and Pharmacology*. Springer International Publishing; 2019. Barrett JE, ed. *Handbook of Experimental Pharmacology*, vol 253; 6. Marshall L, et al. *Int Rev Neurobiol*. 2002;52:93-131; 7. Irwin MR, et al. *Biol Psychiatry*. 2016;80(1):40-52. 8. Imeri L, Opp MR. 2009. Nature Rev, Neuroscience 10: 199-210

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Impact of Impaired Daytime Functioning [1,2]

Workplace Absenteeism and Presenteeism

200,000

Workdays missed[a]

Around **30bn** annual cost of lost sleep to UK

Increased Risk of Injury

+25-30%

increased risk of injury working night shifts than working day shifts

Health Risks

+30%

Adults sleeping <7hrs per night are 30% more likely to be obese

+13%

Adults sleeping <6hrs per night are at a 13% higher mortality risk

1. Varney J. UK Health Security Agency. Updated Jan 2018. Accessed January 10, 2023. Is lack of sleep affecting your work? - UK Health Security Agency (blog.gov.uk)
2. Hafner M et al, RAND 2016. Accessed January 10, 2023. Why sleep matters — the economic costs of insufficient sleep: A cross-country comparative analysis | RAND

Insomnia symptoms and prevalence

Unsatisfactory sleep despite opportunity

1. Subjective complaint of unsatisfactory sleep due to:
   - Difficulty falling asleep
   - Waking up at night and having trouble maintaining sleep
   - Waking up too early and not being able to return to sleep
   - Combination of the above
2. Report of daytime functioning impairments

- Sleep-onset insomnia seems to be more prevalent in younger adults, whereas sleep-maintenance disturbances are more common in middle-aged or older adults
- Age, sex, and potentially ethnicity are factors associated with the prevalence of insomnia
- Older patients tend to report their sleep disturbance and effects on daytime functioning less
- Insomnia is bidirectionally related to other medical comorbidities, such as major depressive disorder, anxiety disorder, hypertension, and substance use

BAP consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders, 2019

Reaching a diagnosis

Clinical assessment

- Complaint of unsatisfactory sleep — sleep onset, sleep maintenance, early waking
- Complaint must be present ≥3 nights/week, ≥3 months and impaired day-time functioning
- There is no objective test for diagnosis; it must rely on diagnostic criteria, clinical observations and use of validated rating scales

Sleep environment and behaviour

- Characterising routine sleep environment and behaviour by asking the patients about their sleep
- Administering clinical rating scales such as the Epworth Sleepiness Scale (ESS) allows assessment of severity and impact on daytime functioning

Medical history

- Investigating past and present medical history
- Determining if another sleep disorder or physical, psychiatric, neurological disorder is present alongside insomnia
- Considering the interplay between conditions

Sleep diary

- Providing a sleep diary to capture the sleep difficulties over time and understand the extent of daytime impairment
- Allowing the patients to capture the nature and severity of their sleep disorder, including sleep efficiency and number of awakenings

Medication and substance use

- Listing past and present medication or substance use
- Optimising treatment of other medical conditions and insomnia
- Understanding the impact of medication or substances in sleep architecture or behaviour

BAP consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders, 2019
National Institute for Health and Care Excellence (NICE), 2021

Example Sleep Diary

Sleep Diary *Start date: / /* *Name: ……*

	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY	SUNDAY
Last night I went to bed at… And turned the lights out (tried to go to sleep at)…							
After turning the lights out I fell asleep in … minutes (estimate)							
I woke up … times in the night							
On each waking during the night I was awake for … minutes (estimate)							
I woke up at … (time of last waking)							
I got out of bed at…							
Overall my sleep last night was (0 = very sound; 8 = very restless)							
When I got up this morning I felt (0 = refreshed; 8 = exhausted)							
Comments … reasons for a particularly good or bad nightly sleep (e.g. bed time change / worries etc).							
Total time asleep							
Total time in bed							

This diary is designed to be reasonably quick to fill in. It is best to fill it in when you wake up in the morning. An estimation of your sleep is fine. It is best to not record the number of times you wake up or try to remember it during the night as it may interfere with your sleep.

Available at: https://www.ouh.nhs.uk/chronic-fatigue/treatment/documents/documents/sleepdiary.pdf [Accessed 2024]

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What is NOT insomnia?

Not all sleepless patients have insomnia

- *Insomnia is getting insufficient sleep, not caused by another sleep disorder, despite adequate opportunity, that leads to daytime consequences*
- Insufficient sleep due to insufficient opportunity is sleep deprivation. The treatment is increasing opportunity
- Insufficient sleep can be caused by restless legs, circadian rhythm disorders etc. The treatment for these is different from insomnia
- Short sleep that doesn't lead to daytime consequences is not insomnia – the person is just a naturally short sleeper

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association Publishing; 2013.

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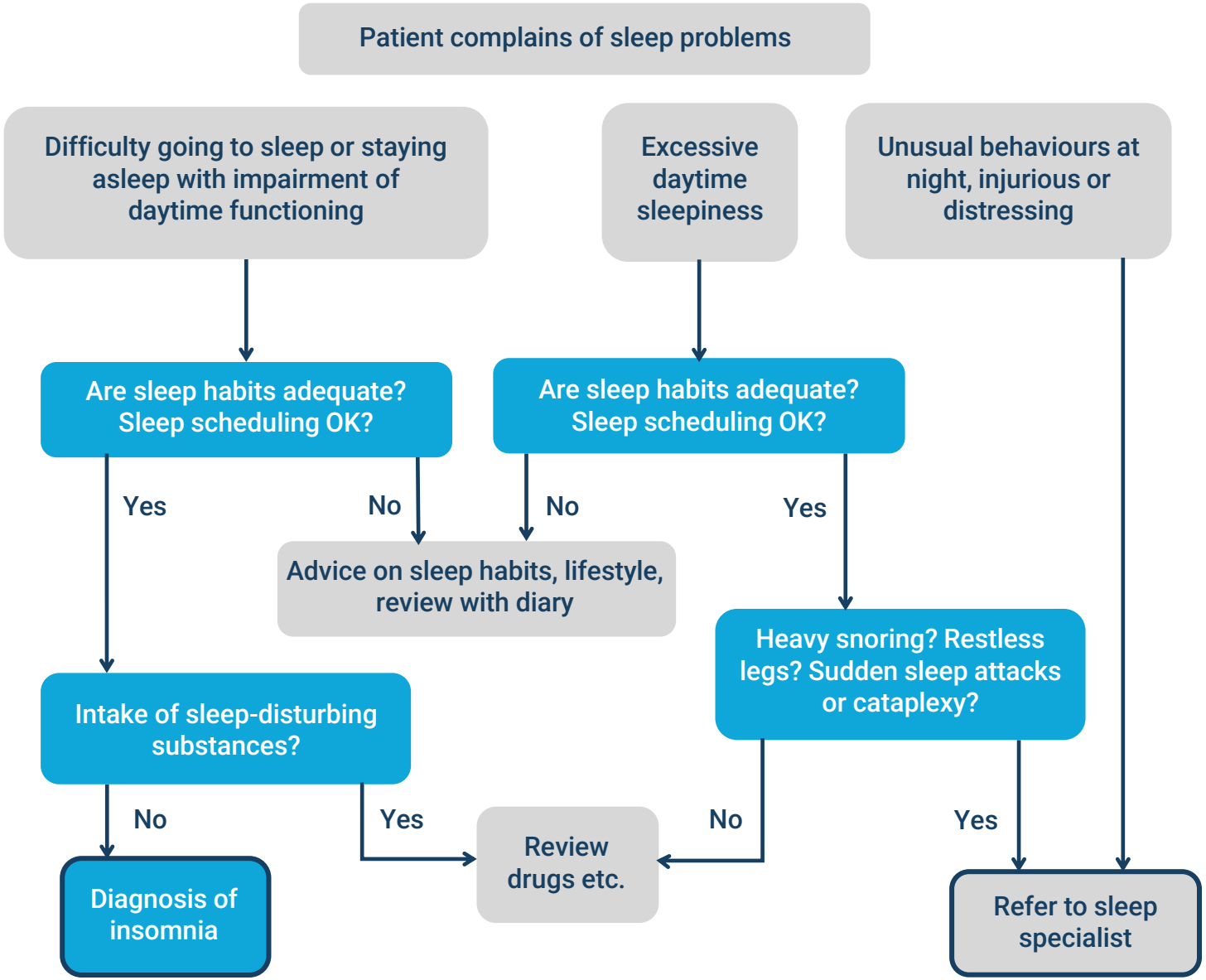
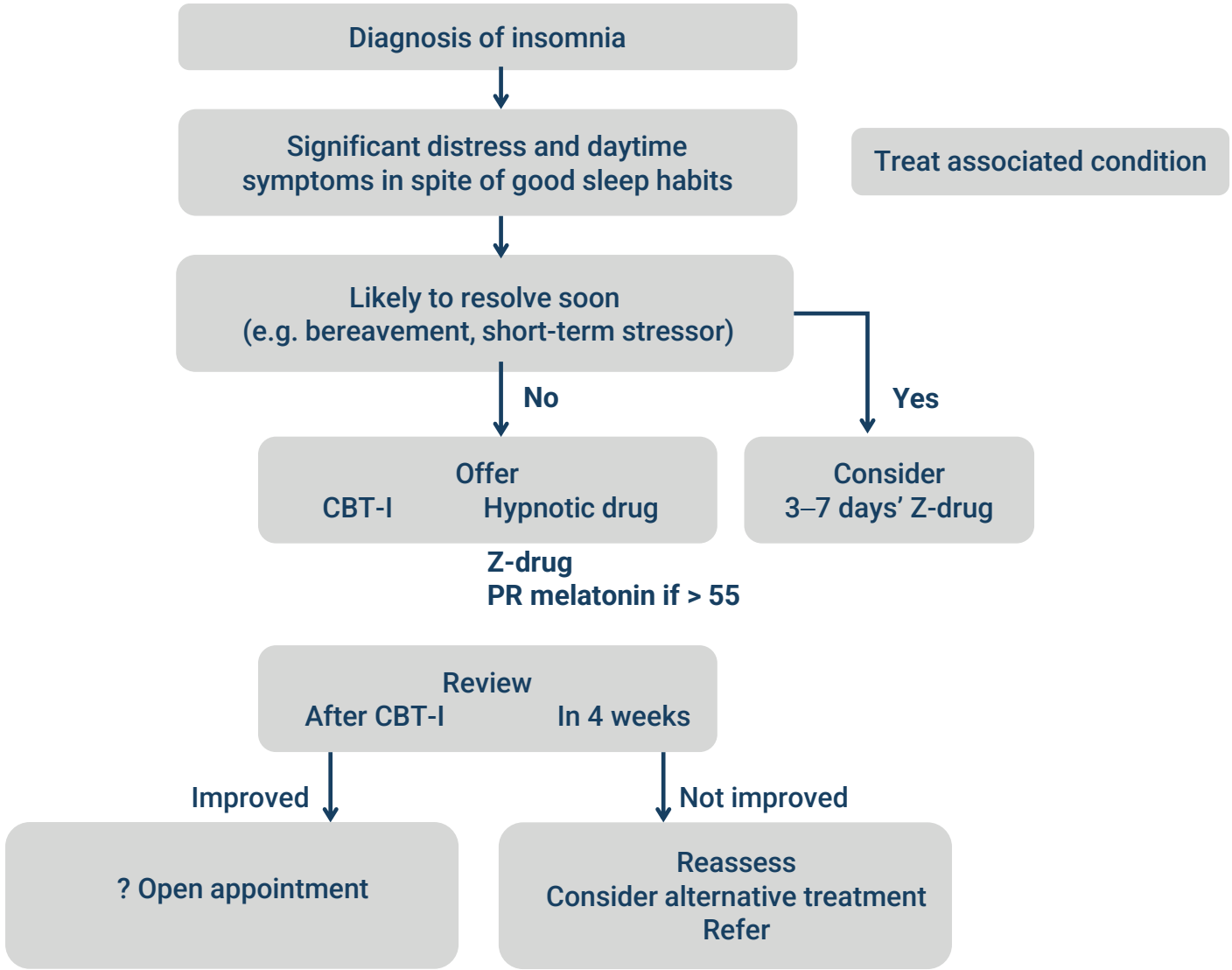
BAP guidelines 2019 – diagnosis of insomnia



BAP consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders, 2019

BAP guidelines 2019 – treatment of insomnia

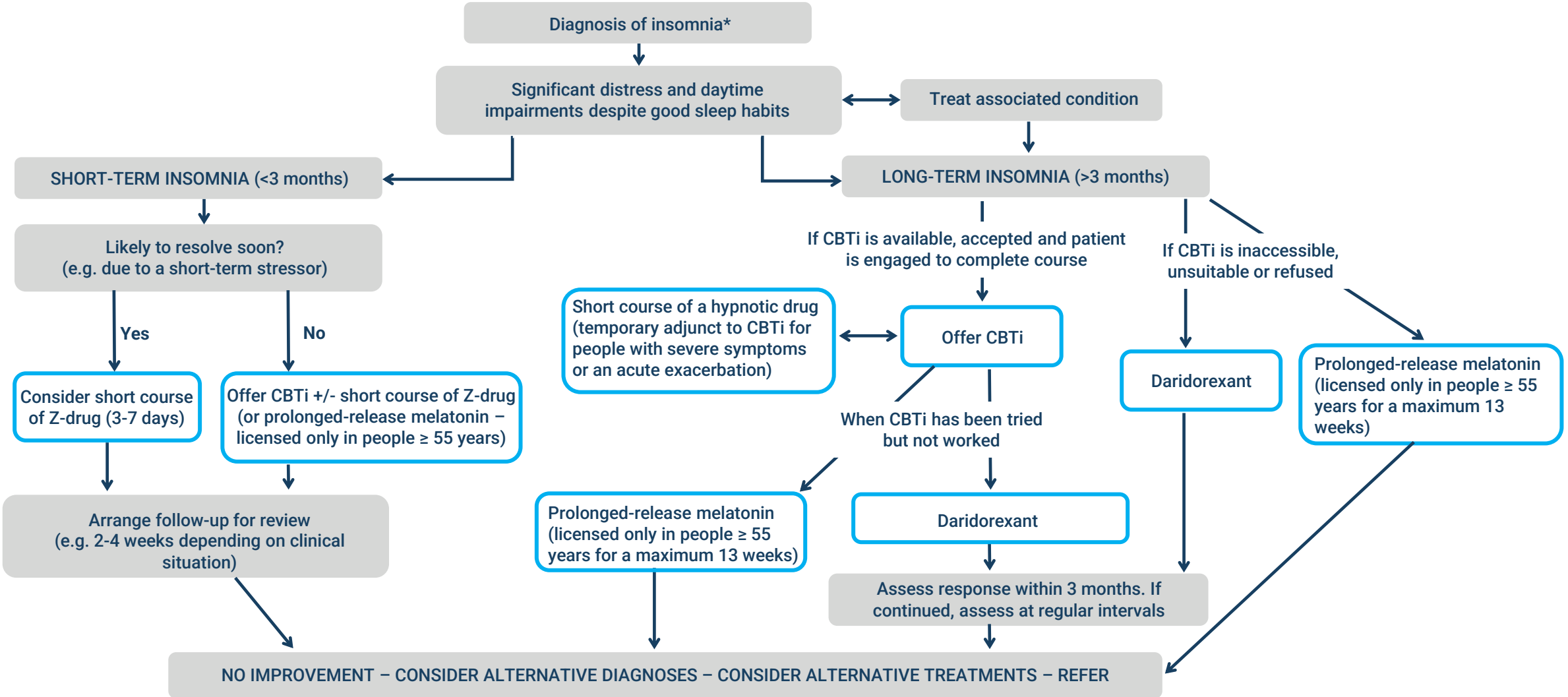


CBT-I, cognitive behavioural therapy for insomnia; PR, prolonged release.

BAP consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders, 2019

Managing Insomnia: NICE Clinical Knowledge Summary

Please refer to the full CKS NICE insomnia update (April 2024) available at: Scenario: Managing insomnia | Management | Insomnia | CKS | NICE[1]

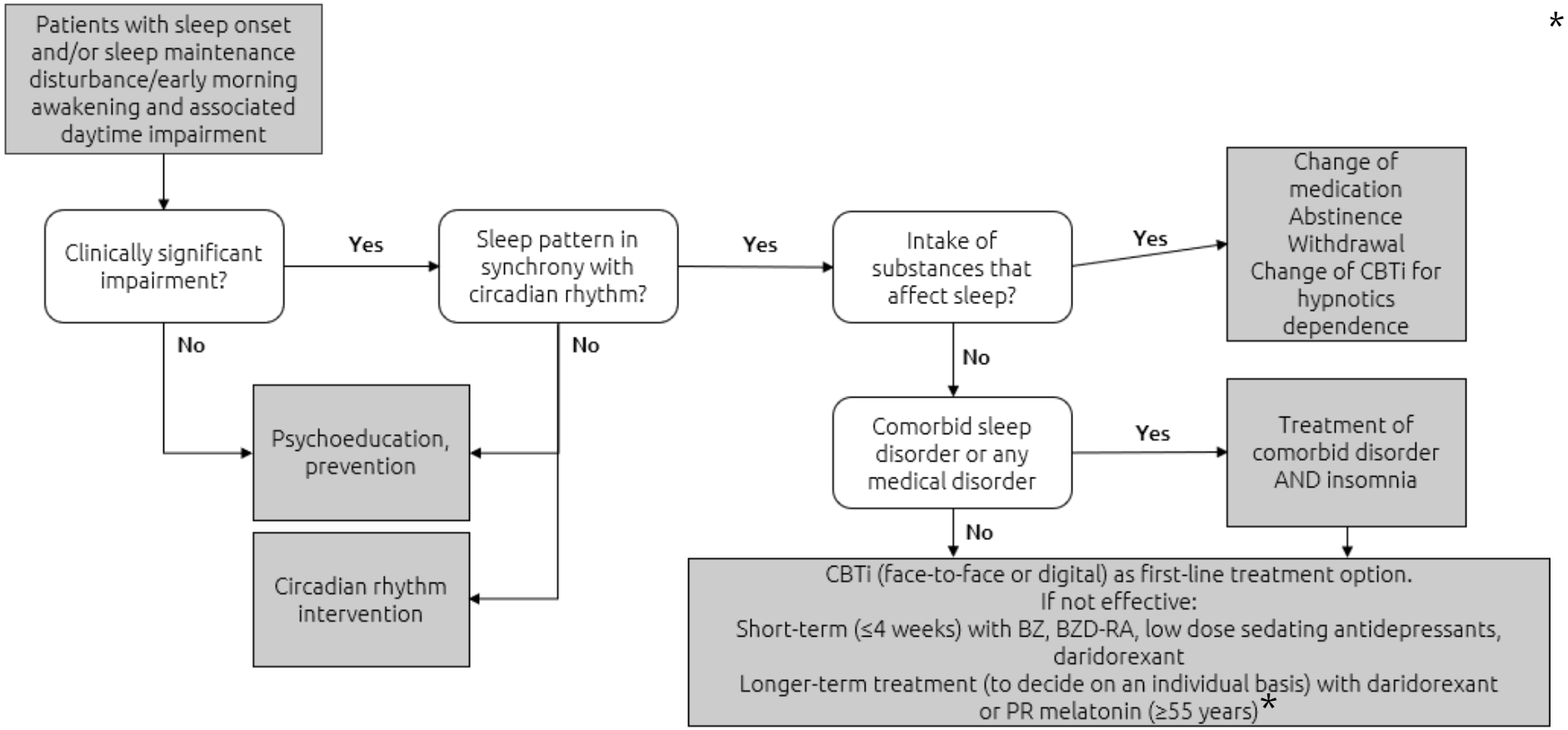


*Consider the need for referral to a sleep clinic or neurology if symptoms of another sleep disorder are present. Address any circumstances/stressors associated with onset of insomnia. Ensure comorbidities (for example anxiety or depression) are optimally managed. Offer advice on sleep hygiene. Advise the person not to drive if they feel sleepy.

CBTi, cognitive behavioural therapy for insomnia

[1] Insomnia | Health topics A to Z | CKS | NICE – NICE CKS Insomnia April 2024 update (accessed 20/05/2024)

2023 European guideline for the diagnosis and treatment of insomnia: Clinical algorithm



* Guidance on longer-term treatment options:

- Orexin receptor antagonists can be used for a period of up to 3 months in the treatment of insomnia (A)
- Longer-term treatment of insomnia disorder with orexin receptor antagonists may be initiated in some cases, and the advantages and disadvantages need to be discussed on an individual basis (A)
- Longer-term treatment of insomnia disorder with PR melatonin (in patients > 55 years) up to 3 months may be effective in some cases (B)

There were four steps of recommendations for this update, ranging from A (very strong recommendation), B (strong), C (weak) to D (very weak recommendation)
BZD, benzodiazepine; BZD-RA, benzodiazepine-receptor agonist; CBTi, cognitive behavioral therapy for insomnia; PR, prolonged-release.
Riemann D, et al. J Sleep Res. 2023; https://doi.org/10.1111/jsr.14035

First-line Treatment for Insomnia Disorder Is CBT-I[5]

- CBT-I is the recommended first-line therapy for insomnia disorder[1-4]
  - CBT-I is effective in adults of all ages, with and without comorbidities, when programs are completed and recommendations are followed. Some severe comorbidities may make some patients unsuitable for CBT-I at a particular time[6]
  - CBT-I can be combined with pharmacological therapy

Therapy[1]	Description[1]
Sleep hygiene	• Teaches healthy lifestyle practices (eg, schedule; avoid naps, stimulants, and alcohol) • Recommended in combination with other behavioral approaches
Sleep restriction therapy	• Time spent in bed is limited to the total sleep time • Increases sleep drive, causing sleep to be more consolidated
Stimulus control	• Eliminate the negative association between bed and undesirable outcomes (eg, wakefulness, frustration) • Strategies include only going to bed when sleepy, getting up after being awake for ~20 minutes, and avoiding clock-watching
Relaxation training	• Techniques for relaxation (eg, progressive muscle relaxation, abdominal breathing) • Goal to lower somatic and cognitive arousal states
Cognitive therapy	• Helps patient identify misinformed, overvalued or maladaptive sleep-related beliefs (explicit or implicit) through evidence of their validity. Develops responses to cope with or overcome them • Decreases worry and effort to sleep

1. Schutte-Rodin S, et al. *J Clin Sleep Med*. 2008;4(5):487-504; 2. Koffel E, et al. *J Gen Intern Med*. 2018;333(6):955-962; 3. Qaseem A, et al. *Ann Intern Med*. 2016;165(2):125-133; 4. Riemann D, et al. *J Sleep Res*. 2017;26(6):675-700. 5. National Institute for Health and Care Excellence (NICE), 2021, 6. BAP consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders, 2019

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The advantages of CBT-I

- Can be delivered individually or in a group setting, either face-to-face or digitally by qualified providers
- Fewer side effects than traditional pharmacological treatments[1]
- Increasing access (especially through digital CBTi)[2]
- A self-management approach[1]
- Impact on other domains (anxiety, depression, pain, QoL, and daytime)[3–6]

CBTi, cognitive behavioral therapy for insomnia; QoL, quality of life.

1. Cheung JMY, et al. Sleep Med Clin. 2019;14:253–65; 2. Cognitive Behavioral Therapy for Insomnia (CBT-I): An Overview. Sleep Foundation. 2023. Available at: https://www.sleepfoundation.org/insomnia/treatment/cognitive-behavioral-therapy-insomnia (accessed November 2023); 3. Hertenstein E, et al. Sleep Med Rev. 2022;62:101597; 4. Selvanathan J, et al. Sleep Med Rev. 2021;60:101460; 5. Benz F, et al. Clin Psychol Rev. 2020;80:101873; 6. Alimoradi Z, et al. Sleep Med Rev. 2022;64:101646; 7. Baglioni C et al. J Sleep Res 2023:e14016; 8. Ong JC, et al. J Psychosomatic Research. 2008;64:419–25; 9. Koffel E, et al. J Gen Intern Med. 2018;333:955–962; 10. Morin CM, et al. JAMA;301:2005–2015; 11. Information based on speaker's clinical opinion.

Challenges with CBT-I adoption[1-6]

In-person not readily accessible to patients[1-4]

- Limited number of qualified providers[1]
- Lack of HCP referrals[2-4]

Insufficient therapy for many[6]

- Up to 40% do not complete program[a]
- 48%-53% do not follow recommendations

May **be ineffective**[6-8]

- May be ineffective for 20%-40% of patients, even among those who complete the program[6,7]
- Efficacy declines over time[8]

[a]A high degree of effort and self-discipline is needed to fully commit to the therapy.

1. Thomas A, et al. *Behav Sleep Med*. 2016;14(6):687-698; 2. Driot D, et al. *Therapie*. 2019;74(5):537-546; 3. Everitt H, et al. *Br J Gen Pract*. 2014;64(619):e112-e119; 4. Conroy DA, Ebben MR. *Behav Neurol*. 2015;2015:819402; 5. Schutte-Rodin S, et al. *J Clin Sleep Med*. 2008;4(5):487-504; 6. Koffel E, et al. *J Gen Intern Med.* 2018;333(6):955-962; 7. Morin CM, et al. *JAMA*. 2009;301(19):2005-2015. 8. van der Zweerde T, et al. *Sleep Med Rev*. 2019;48:101208.

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Treatment

Pharmacological options

↑ Enhance sleep
GABA, Melatonin

- Benzodiazepines
- Z drugs
- Melatonin

↓ Reduce wakefulness
Histamine, Noradrenaline, Serotonin, Acetylcholine, Dopamine, Orexin

- Dual Orexin Receptor Antagonists

Off-label/OTC options:

- Low-dose sedating antidepressants
- Antihistamines
- Antipsychotics

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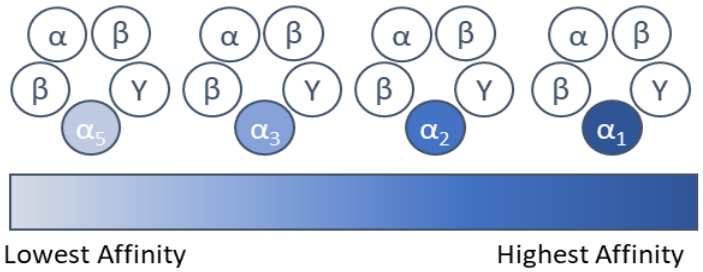
https://www.ema.europa.eu/en/medicines/human/EPAR/quviviq, https://products.mhra.gov.uk/product/?product=QUVIVIQ

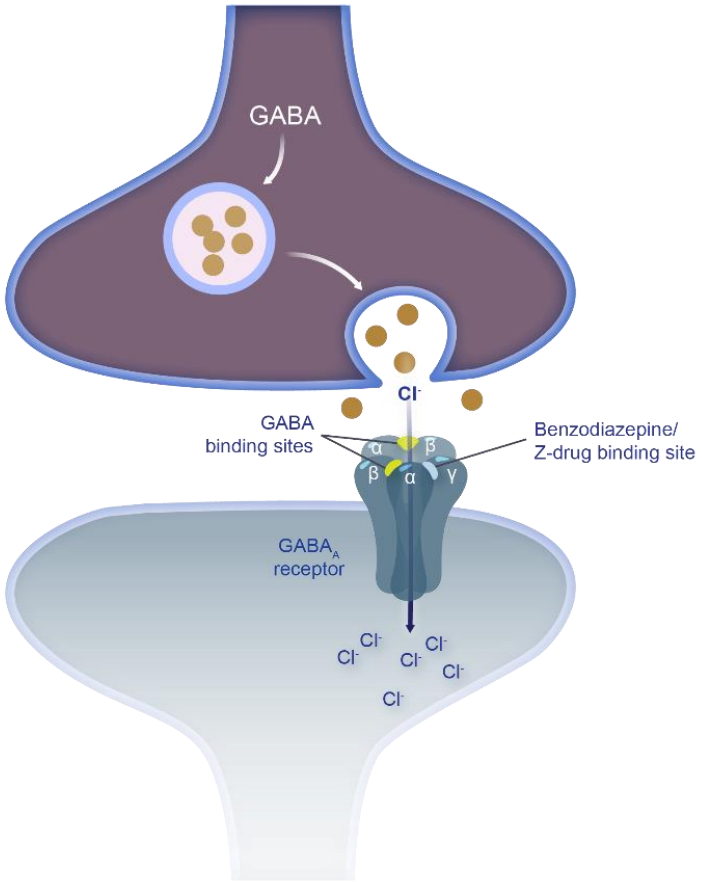
Mechanism of action of benzodiazepines and Z-drugs

- **Benzodiazepines** are positive allosteric modulators of GABA receptors. They tend to bind all type A ($GABA_A$) receptor subtypes with similar affinity[4]
  - $GABA_A$ receptors are widely expressed throughout the CNS[5]
- Benzodiazepines are considered non-specific drugs with a wide range of clinical effects[1,6]
  - For example, sedation, anxiety reduction, seizure inhibition, and muscle relaxation
- **Z-drugs**, also known as non-benzodiazepines, have a similar mechanism of action to benzodiazepines but have higher affinity for the $GABA_A$ α1 receptor subtype than for other type α subtypes[1-3,8]
  - $GABA_A$ α1 receptor subtype is preferentially expressed in the cortex and has been shown to mediate hypnotic action[6,7]

Zolpidem $GABA_A$ Subunit Binding Affinity[5]



Mechanism of Action of Benzodiazepines and Z-drugs[2-4,7]



CNS = central nervous system; GABA = gamma aminobutyric acid; GABA-RA - γ-Aminobutyric acid receptor agonist

1. Krystal AD, et al. *World Psychiatry*. 2019;18(3):337-352; 2. Landolt H-P, et al, eds. *Sleep-Wake Neurobiology and Pharmacology*. Basel, Switzerland: Springer International Publishing; 2019.
3. Scammell TE, et al. *Annu Rev Pharmacol Toxicol*. 2011;51:243-266; 4. Kryger MH, et al, eds. *Principles and Practice of Sleep Medicine*. 6th ed. Amsterdam, The Netherlands: Elsevier; 2017.
5. Crowe SF, Stranks EK. *Arch Clin Neuropsychol*. 2018;33(7):901-911; 6. Bounds CG. *StatPearls [Internet]*. Treasure Island, FL: StatPearls Publishing; 2021;
7. Möhler H. Benzodiazepines. In: *Encyclopedia of Life Sciences*. Chichester, UK: John Wiley & Sons, Ltd; 2005. 8. Asnis GM, et al. *Int J Mol Sci*. 2016;17(1):50;

Benzodiazepine and Z-drug use considerations

Effective in the short-term (≤4 weeks) treatment[1]

Over an extended period, tolerance and Impairment of cognitive function may occur[2-3]

Benzodiazepines are effective in reducing Sleep Onset Latency and increasing sleep duration[4], whereas Z-drugs have been shown to improve Sleep Onset Latency[5]

A few studies have provided some evidence of patient-reported daytime symptom improvement with Z-drugs[6]

- Z-drugs showed significantly better patient-reported daytime alertness, ability to function during daytime, and physical sense of well-being than placebo
- However, such studies used patient-reported outcomes instruments that were not validated according to FDA guidelines[7]

1. Asnis GM, et al. *Int J Mol Sci*. 2016;17(1):50; 2. Crowe SF, Stranks EK. *Arch Clin Neuropsychol*. 2018;33(7):901-911; 3. Möhler H. Benzodiazepines. In: *Encyclopedia of Life Sciences*. Chichester, UK: John Wiley & Sons, Ltd; 2005. 4. Landolt H-P, et al, eds. *Sleep-Wake Neurobiology and Pharmacology*. Basel, Switzerland: Springer International Publishing; 2019 5. Huedo-Medina TB, et al. *BMJ*. 2012;345:e8343; 6. Kryger MH, et al, eds. *Principles and Practice of Sleep Medicine*. 6th ed. Amsterdam, The Netherlands: Elsevier; 2015. 7. Hudgens S, et al. *Patient*. 2021;14(2):249-268

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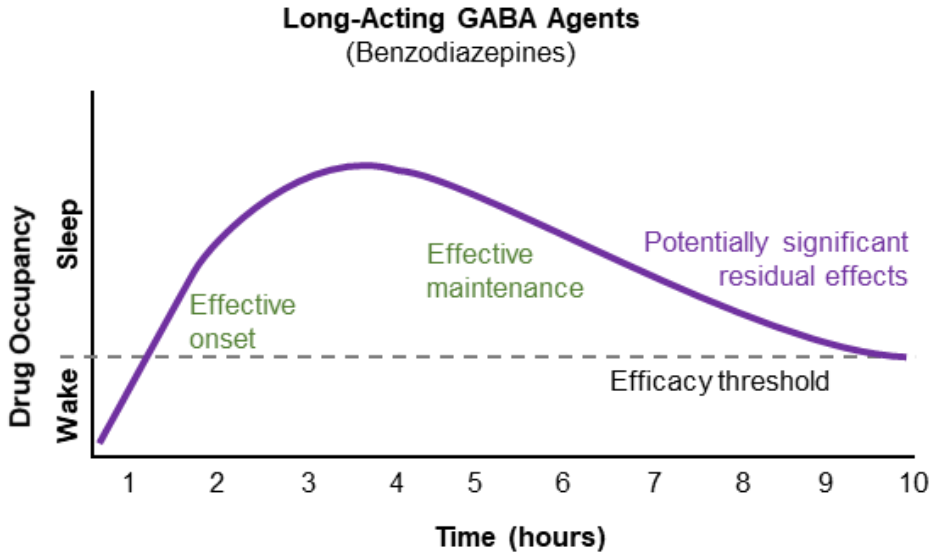
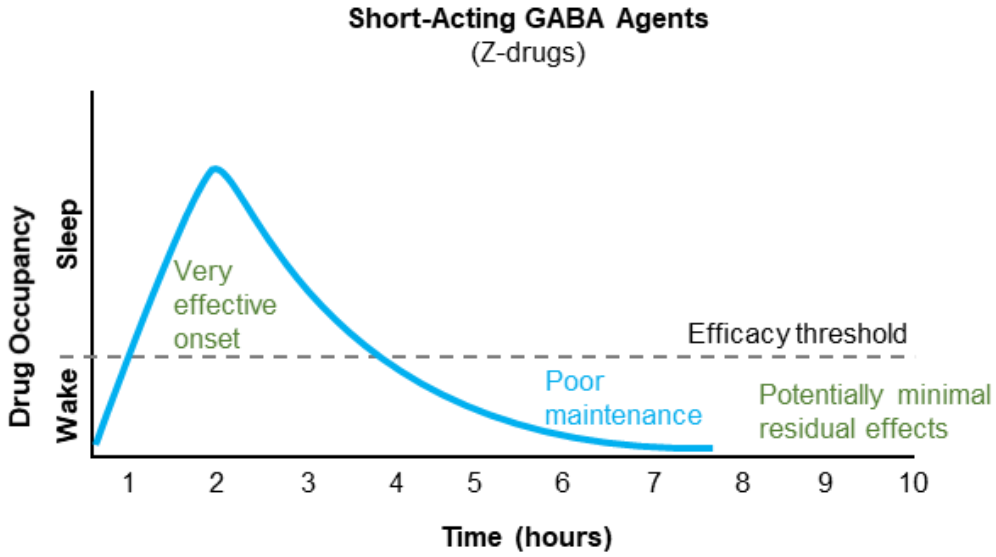
Considerations with short- and long-acting GABA agents





- Following treatment with long-acting GABA agents, the drug receptor occupancy exceeds that required for sleep efficacy, which in turn may lead to significant residual effects[1,2]
- On the other hand, short-acting GABA agents might not be sufficient to engage the receptors, which may allow for early morning awakenings[1,2]

Note: benzodiazepines tend to **reduce slow-wave sleep** but have **no effect on REM sleep**[3]

REM = rapid eye movement.

1. Gotter AL, et al. *BMC Neurosci*. 2013;14:90. doi: 10.1186/1471-2202-14-90; 2. Asnis GM, et al. *Int J Mol Sci*. 2016;17(1):50. doi: 10.3390/ijms17010050; 3. Kryger MH, et al, eds. *Principles and Practice of Sleep Medicine*. 6th ed. Amsterdam, The Netherlands: Elsevier; 2015.

Use of modified-release (MR) melatonin in insomnia

- Melatonin is an endogenous hormone produced in the pineal gland involved in the regulation of circadian rhythms and wake-sleep patterns[1,2,3]
  - Its production declines with age and is lower in middle-aged and elderly patients with insomnia than in good sleepers [3]
  - Melatonin receptor agonists are commonly used to treat insomnia by promoting sleep onset

Characteristics of MR melatonin [3]

Melatonin	Dose range (mg)*	Maximum dose (mg)†	Time to maximum concentration (h)	Half-life (h)	Mechanism of action	Metabolism	Contraindications	Common side-effects
Melatonin	1–3	2	1·6	3·5–4	Melatonin agonism of MT1, MT2, and MT3 receptors	*CYP1A1; CYP1A2; CYP2C19*	Hypersensitivity to melatonin or other component of the product (eg, excipents)	Back pain, arthralgia, weakness

Licensed indication for MR melatonin in the UK is for short-term use[4]: adults over 55 years of age, 2mg once daily for up to 13 weeks

1. Kryger MH, et al, eds. *Principles and Practice of Sleep Medicine*. 6th ed. Amsterdam, The Netherlands: Elsevier; 2015; 2. Landolt H-P, et al, eds. *Sleep-Wake Neurobiology and Pharmacology*. Basel, Switzerland: Springer International Publishing; 2019. 3. Perlis *et* al, Lancet 2022; 400: 1047–60 4. British National Formulary (2022)

Treatment

Pharmacological options

↑ Enhance sleep
GABA, Melatonin

- Benzodiazepines
- Z drugs
- Melatonin

↓ Reduce wakefulness
Histamine, Noradrenaline, Serotonin, Acetylcholine, Dopamine, Orexin

- Dual Orexin Receptor Antagonists

Off-label/OTC options:

- Low-dose sedating antidepressants
- Antihistamines
- Antipsychotics

BAP consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders, 2019
https://www.ema.europa.eu/en/medicines/human/EPAR/quviviq, https://products.mhra.gov.uk/product/?product=QUVIVIQ

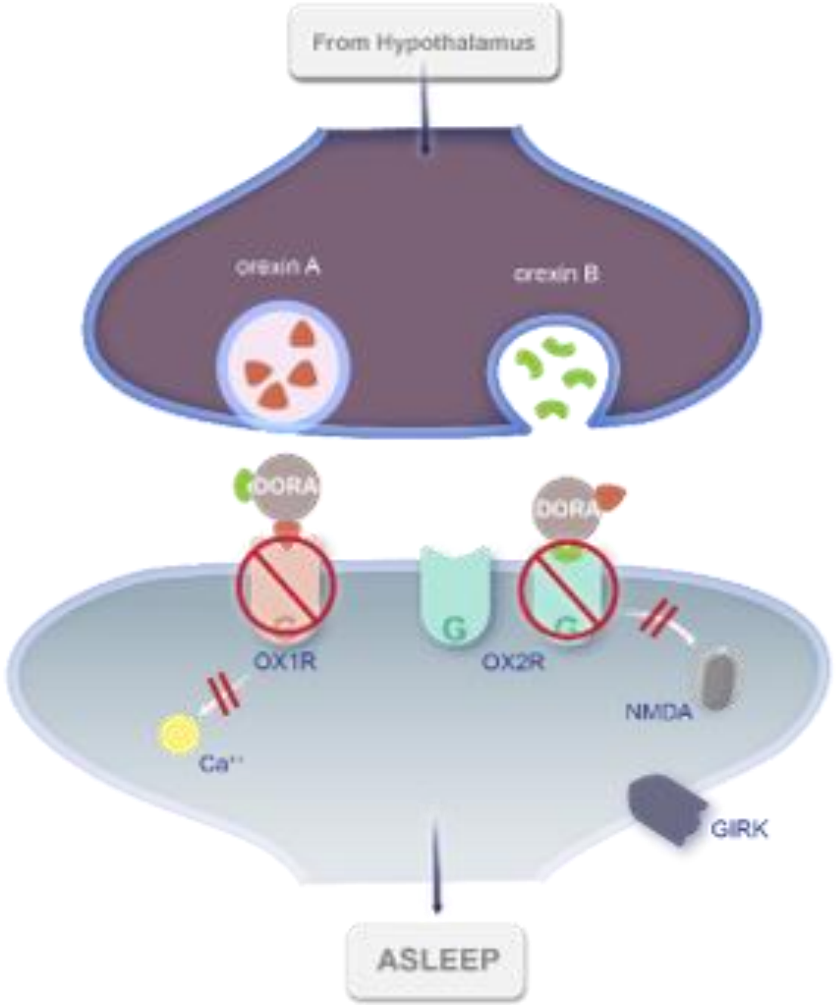
How to target orexin?

Dual Orexin Receptor(s) Antagonists (DORAs)

- The Orexin system promotes wakefulness
  -> antagonism of orexin receptors allows sleep to occur

- Orexin-A and -B are derived from orexin-containing neurons located in the hypothalamus
- The activity of orexin-A and -B is modulated by their specific receptors, OX1R and OX2R
- Binding of orexin-A and -B to the target receptors excites target neurons in the wake-promoting brain regions

- DORAs specifically target the orexin system and block the binding of wake-promoting orexin-A and -B to receptors (OX1R and OX2R) to suppress the wake drive



Alexandre C, et al. 2013, Curr Opin Neurobiol, 23(5):752–759, Chieffi S, et al. 2017, Front Physiol, 8:357, Wang C, et al. 2018, Front Mol Neurosci, 11:220; Scammell TE, et al. 2017, Neuron, 93(4):747–765, Muehlan C, et al. J Clin Psychopharmacol. 2020;40(2):157-166;

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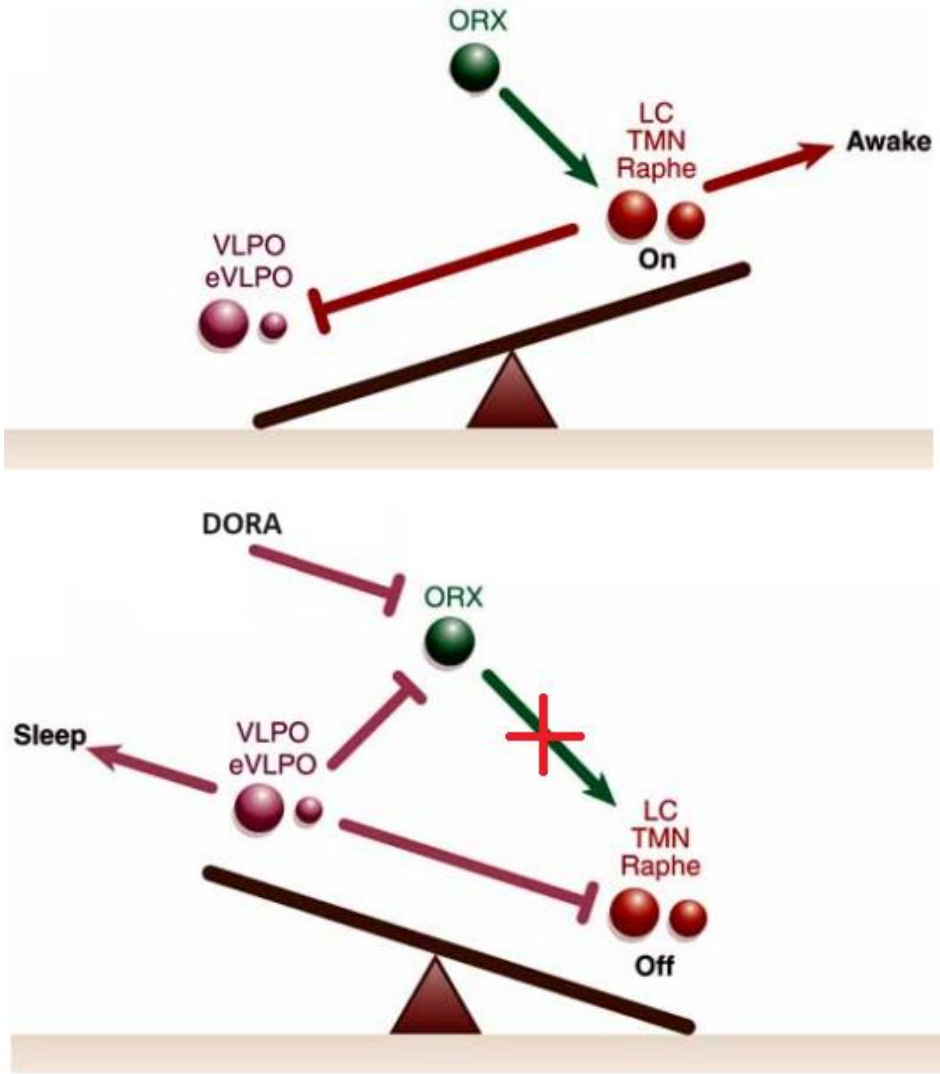


Adapted from: Schwartz.J & Roth.T. Neurophysiology of sleep and wakefulness: basic science and clinical implications (2008). *Current Neuropharmacology* 6:367-378

ORX – orexin; LC – locus coeruleus; TMN – tuberomammillary nucleus; VLPO – ventrolateral preoptic nucleus

Alexandre C, et al. 2013, Curr Opin Neurobiol, 23(5):752–759, Chieffi S, et al. 2017, Front Physiol, 8:357, Wang C, et al. 2018, Front Mol Neurosci, 11:220; Scammell TE, et al. 2017, Neuron, 93(4):747–765, Muehlan C, et al. J Clin Psychopharmacol. 2020;40(2):157-166;

Use of daridorexant in insomnia

After 3 months, compared to placebo, daridorexant reduced sleep onset latency (SOL), reduced wake time after sleep onset (WASO), increased self-reported total sleep time, and improved daytime functioning, as measured by the IDSIQ questionnaire sleepiness domain[1]

Efficacy was sustained at 12 months [2]

No evidence of rebound insomnia, withdrawal effects or TEAEs that would suggest drug abuse potential [1-2]

Approved doses (mg)	Time to maximum concentration (h)	Half-life (h)	Metabolism	Contraindications	Common side-effects
25, 50	1-2	6-10	CYP3A4	Hypersensitivity to daridorexant or any of the excipients, narcolepsy, strong CYP3A4 inhibitors	Headache, somnolence, dizziness, nausea, fatigue

Daridorexant is indicated for the treatment of adult patients with insomnia characterised by symptoms present for at least 3 months with considerable impact on daytime functioning[3]

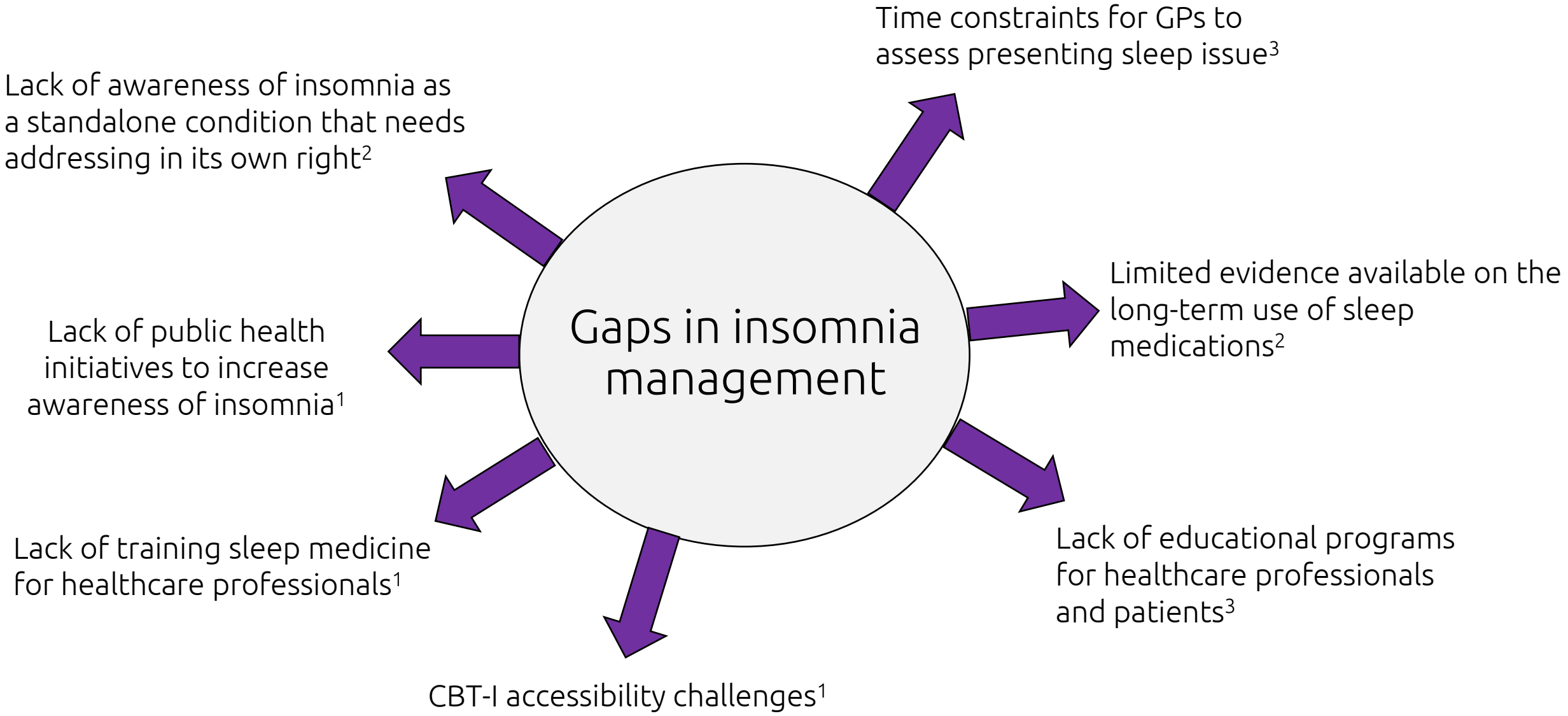
TEAEs - treatment emergent adverse events

[1] Mignot E, et al. Lancet Neurol. 2022;21:125–39
[2] Kunz D, et al. CNS Drugs 2022; doi: 10.1007/s40263-022-00980-8
3 Daridorexant SmPC

Off-label and over-the-counter options: antidepressants, antihistamines and antipsychotics

Low-dose sedating antidepressants	Antihistamines	Antipsychotics
Frequently used in managing both insomnia and comorbid insomnia	Readily available over the counter	Generally not recommended for the treatment of insomnia without comorbidities, in either the short or long term
Significant but small effects have been noted for doxepin and trazodone in the short term, up to 4-weeks	Typically well tolerated, possibly useful for mild short-term insomnia, but generally not recommended	Potentially helpful for comorbid psychosis or depression
They have a considerable impact on sleep architecture	Tolerance can readily develop	Can be associated with weight gain
They have long half-lives, which may lead to daytime sedation	They have long half-lives, which may lead to daytime sedation	They have long half-lives, which may lead to daytime sedation

Riemann D, et al. J Sleep Res. 2023; https://doi.org/10.1111/jsr.14035;
BAP consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders, 2019
https://www.ema.europa.eu/en/medicines/human/EPAR/quviviq, https://products.mhra.gov.uk/product/?product=QUVIVIQ



1, Hafner et al RAND Corporation, 2016. https://www.rand.org/pubs/research_reports/RR1791.html. 2 Riemann, D. et al. (2017), European guideline for the diagnosis and treatment of insomnia. J Sleep Res, 26: 675-700. https://doi.org/10.1111/jsr.12594 3. Haycock, J., Grivell, N., Redman, A. *et al.* Primary care management of chronic insomnia: a qualitative analysis of the attitudes and experiences of Australian general practitioners. *BMC Fam Pract* **22**, 158 (2021). https://doi.org/10.1186/s12875-021-01510-z

Summary

- Sleep is regulated by the circadian rhythm and homeostatic drive[1]
- The orexin system is the main conductor of the sleep-wake switch[1]
- Predisposing, precipitating, perpetuating factors can contribute to the development and maintenance of insomnia[2]
- Insomnia is associated with several comorbidities and cardiometabolic risk[2]
- CBT-I is the first-line treatment for insomnia in the UK. A number of pharmacological treatments are also available if CBT-I is ineffective or unsuitable[3]

1. Rash B, Born J. 2013. Physiol Rev, 93(2): 681-766; 2. Spielman AJ, *et al. Psychiatr Clin North Am* 1987;10:541-553; 3. National Institute for Health and Care Excellence (NICE),2021 6. British National Formulary (2022);

Thank you

Questions

Evolution of chronic insomnia classification

Classification	Main features[1]	Definition[2]	Frequency[2]
ICD-10 (2010, WHO)	• First applied a frequency criterion and minimum duration • Separates insomnia into primary and secondary (co-morbid)	Difficulty with one or more of the following: - falling asleep - maintaining sleep - non-refreshing sleep	Three times a week and for longer than 1 month
ICD-11 (2015, WHO)	Follows ICSD-3 terminology in having codes for: - chronic insomnia - short-term insomnia - "insomnia disorders, unspecified"	Frequent and persistent difficulty with one or more of the following: - initiating sleep - maintaining sleep - general sleep dissatisfaction - AND some form of daytime impairment[3]	The sleep disturbance and associated daytime symptoms occur at least several times per week for at least 3 months[3]
DSM-5 (2014, APA)	• Consolidates all insomnia variants into the **single** diagnosis of insomnia disorder • The comorbid conditions can be specified without implying causality • One can specify if it is episodic (1–3 months), persistent (>3 months), or recurrent (two or more episodes within 1 year)	Unhappiness with the quality or quantity of sleep, which can include one or more of the following: - trouble falling asleep - staying asleep - waking up early and being unable to get back to sleep - AND associated with impairment to daytime functioning or well-being	Three nights a week for at least 3 months

WHO: World Health Organisation, **APA:** American Psychiatric Association

1. Poon *et al.* "Insomnia Disorders: Nosology and Classification Past, Present, and Future". Available at: https://neuro.psychiatryonline.org/doi/10.1176/appi.neuropsych.20080206 [Accessed February, 2024] 2. BAP consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders, 2019. Available at: https://www.bap.org.uk/pdfs/BAP_Guidelines-Sleep.pdf [Accessed February, 2024] 3. ICD-11 for Mortality and Morbidity Statistics, available at: ICD-11 for Mortality and Morbidity Statistics (who.int) [Accessed February, 2024]

Common Measures in Clinical Trials[1-4]

- Efficacy endpoints, which are typically measured using polysomnography or a sleep diary, are pervasive across clinical trials of insomnia disorder[1]
- Some endpoints can be measured using both objective and subjective tools[1,5]

Objective Endpoint	Definition
Latency to persistent sleep (LPS)	Time to onset of first 10 consecutive minutes of sleep
Wake after sleep onset (WASO)	Total amount of time awake during the night, excluding SOL and amount of time from final awakening to getting out of bed
Total sleep time (TST)	Total time spent sleeping
Sleep efficiency (SE)	Percentage of time in bed spent asleep (SE=[TST/time in bed] × 100)

Subjective Endpoint	Definition
Subjective total sleep time (sTST)	Estimated total time spent sleeping
Subjective sleep onset latency (sSOL)	Estimated time from attempt to sleep until sleep onset Also known as subjective latency to sleep onset (sLSO)
Subjective wake after sleep onset (sWASO)	Estimated time awake during the night after initial sleep onset, until getting out of bed
Subjective sleep efficiency (sSE)	Percentage of time in bed spent asleep (sSE=[sTST/time in bed] × 100)
Subjective Sleep Quality (sSQ)	Patient-reported quality of sleep, typically defined by an ordinal or visual analog scale No objective definition/measure for sleep quality

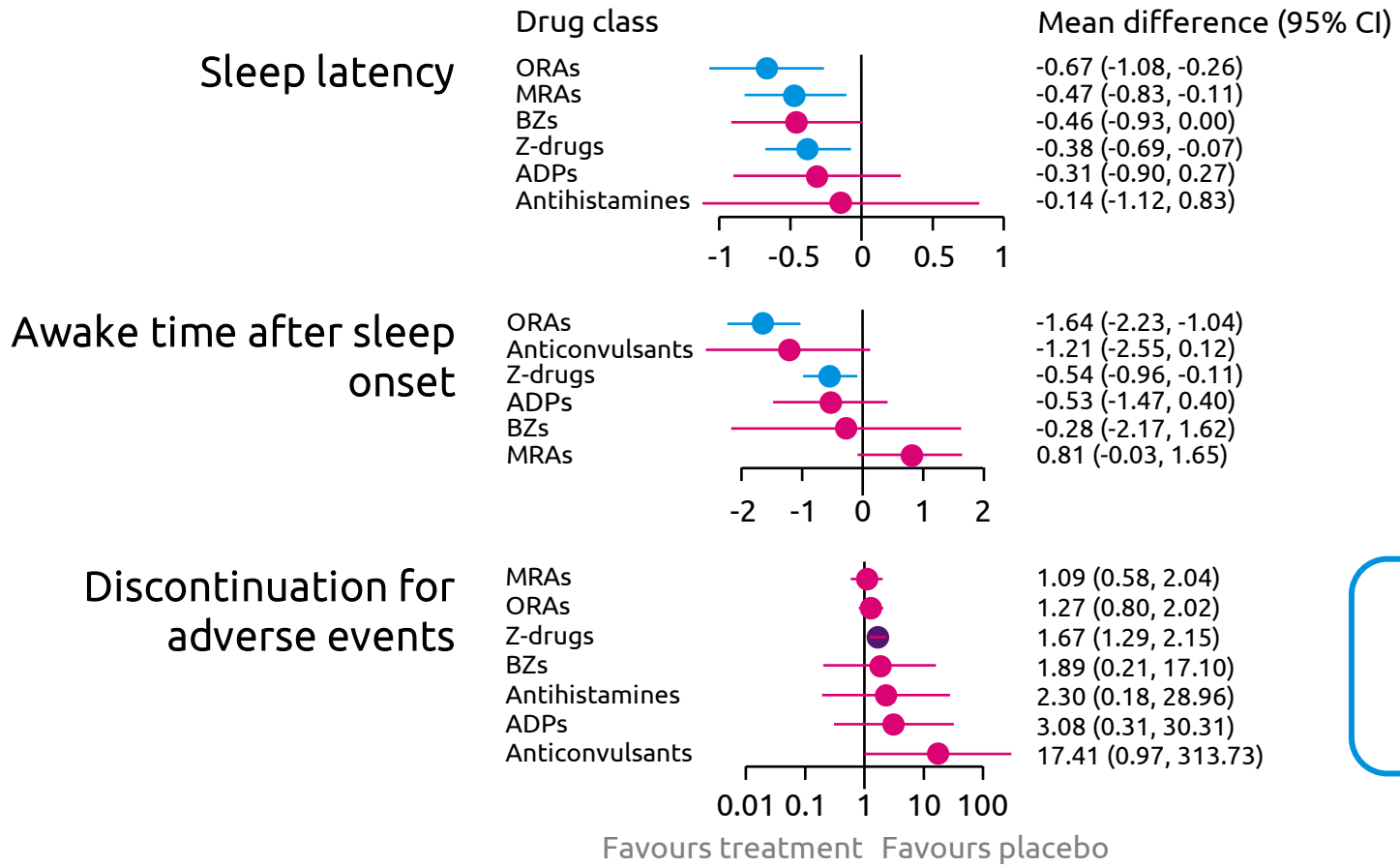
Endpoints in insomnia clinical trials typically assess sleep but rarely assess daytime functioning[1]

SOL = sleep onset latency.

1. Sateia MJ, et al. *J Clin Sleep Med*. 2017;13(2):307-349; 2. Buysse DJ, et al. *Sleep*. 2006;29(9):1155-1173; 3. Rosenberg R, et al. *JAMA Netw Open*. 2019;2(12):e1918254; 4. Schutte-Rodin S, et al. *J Clin Sleep Med*. 2008;4(5):487-504; 5. Kärppä M, et al. *Sleep*. 2020;43(9):zsaa123.

Efficacy and tolerability of insomnia medications

Systematic review and network meta-analysis of placebo-controlled or head-to-head randomised controlled trials for primary insomnia in adults



Indirect comparisons such as network meta-analysis are valuable in the absence of head-to-head studies but may have a higher risk of bias[2]

ADP, antidepressants; MRA, melatonin receptor agonists; ORAs, orexin receptor agonists.

Yue JL, et al. Sleep Med Rev. 2023;68:1017462; 2. Cipriani A, et al. Ann Intern Med. 2013;159:130-7.