CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Migraine and Sleep

James Im, MD, FRCPC

Disclosures: James Im, MD, FRCPC

No financial relationships to disclose.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Learning Objectives

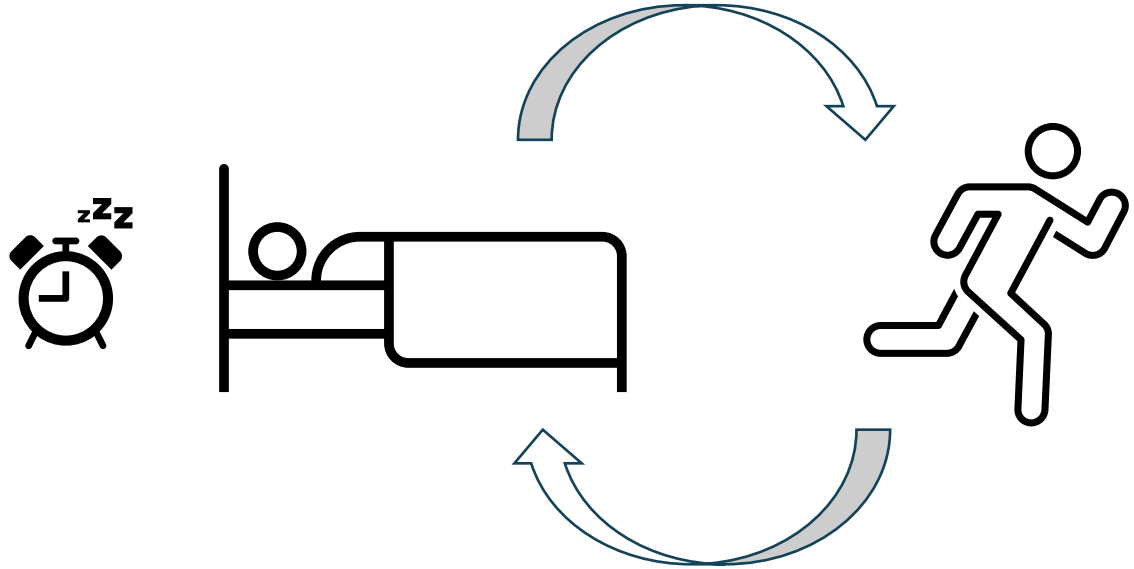
Upon completion of this activity, learners will be able to

- Describe a broad overview of basic sleep physiology
- Be able to obtain a sleep history and describe methods to measure and assess sleep
- Be able to diagnose and describe treatment of insomnia in the context of migraine
- Be able to describe treatment effects of migraine medications on sleep
- Discuss sleep apnea headache, pathophysiology and treatment
- Discuss new discoveries and implications of CGRP and PACAP involving sleep

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

What is Sleep?

- Cyclically reversible state of unconsciousness and unresponsiveness
- Typically, 24 to 26-hour cycles reported (24.1 hour in ‘free running’ cycles)



Castillo PR. Clinical Neurobiology of Sleep and Wakefulness. Continuum (Minneap Minn). 2023 Aug 1;29(4):1016-1030. doi: 10.1212/CON.0000000000001260. PMID: 37590820.

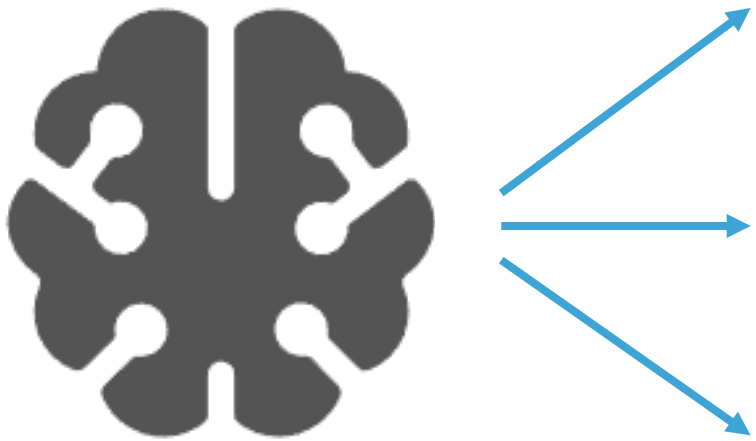
CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Why do we Sleep?

- Development / Ontogeny
- Metabolism
- Immune system regulation
  - (Immune responses including leukocyte mobilization and trafficking, cytokine release, and T-cell differentiation are mediated in a time-of-day–dependent manner)
- Cognition
- Synaptic neuroplasticity and memory consolidation
- Glymphatic waste clearance
- Mood and emotional regulation

Castillo PR. Clinical Neurobiology of Sleep and Wakefulness. Continuum (Minneap Minn). 2023 Aug 1;29(4):1016-1030. doi: 10.1212/CON.0000000000001260. PMID: 37590820.

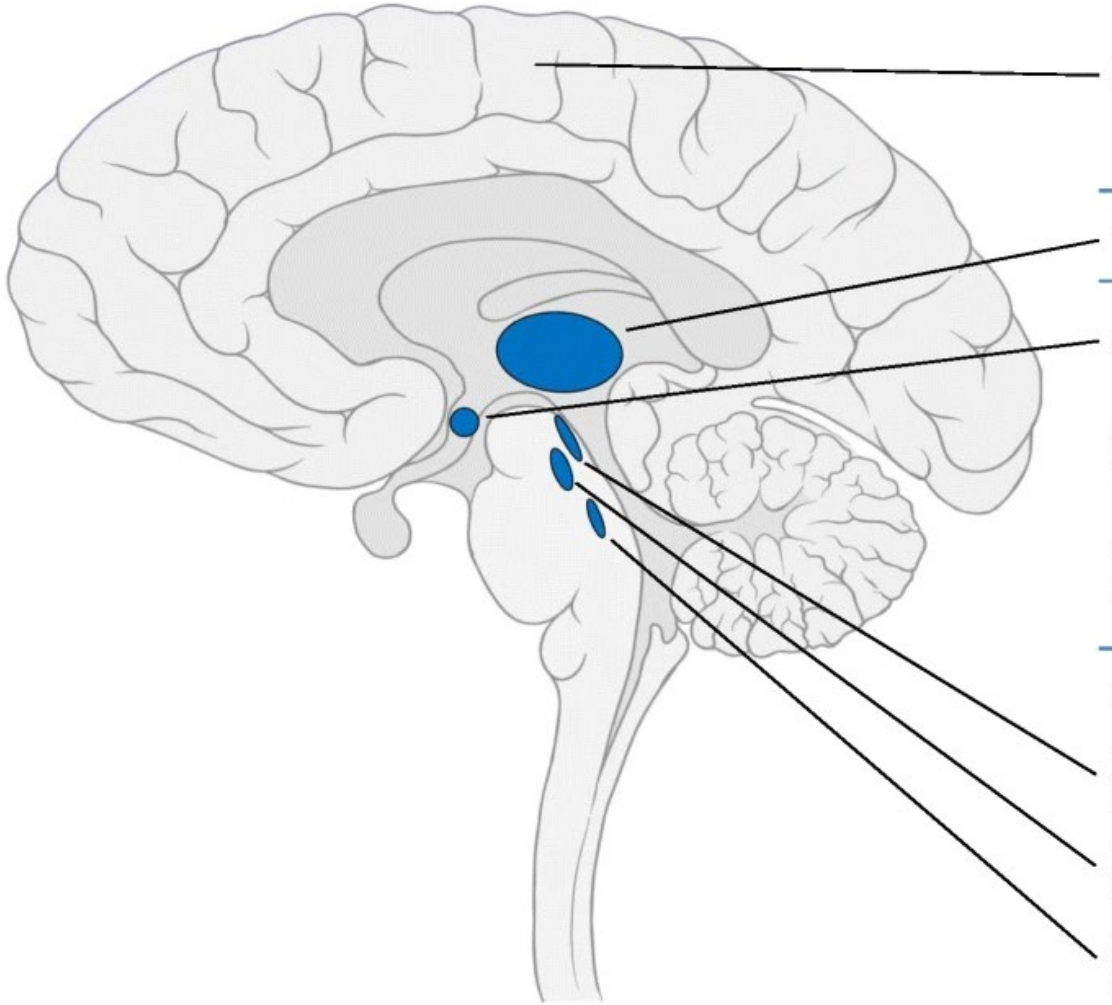
How to Sleep? (Overview)



- Neuroanatomy
- Neurotransmitters
- Circadian Rhythm

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

How Do We Sleep? (Neuroanatomy)



CORTEX	**Promotion of wakefulness** through ascending inputs from monoaminergic neurons, hypothalamus, and basal forebrain
THALAMUS	**Promotion of wakefulness and integration of sub-cortical sleep-wake inputs**
HYPOTHALAMUS	**Promotion of wakefulness, regulation of circadian rhythm and control of sleep-wake transition**
Posterior hypothalamus (dopamine)	**Promotion of wakefulness** through the activation of the brainstem monoaminergic system, the basal forebrain, and the cortex
Lateral hypothalamus (orexin)	**Control of sleep-wake transition:** participate to the "flip-flop" system for sleep-wake transition*, maintain the stability of the waking state, and prevent the inappropriate sudden onset of sleep
BRAINSTEM	**Promotion of wakefulness:** ascending activating pathways projecting from the brainstem to the thalamus and basal forebrain
Periaqueductal gray (dopamine) Dorsal raphe nucleus (serotonin) Locus coeruleus (norepinephrine)	**Stabilization of the waking state:** receive the orexinergic excitatory projections and sends inhibitory inputs to the sleep promoting VLPO to reinforce wakefulness **Control of the transition to sleep:** inhibition of these nuclei by the VLPO promotes sleep. Noradrenergic and serotoninergic neurons inhibit the REM sleep

Odegård SS, Sand T, Engstrøm M, Stovner LJ, Zwart JA, Hagen K. The long-term effect of insomnia on primary headaches: a prospective population-based cohort study (HUNT-2 and HUNT-3). Headache. 2011 Apr;51(4):570-80. doi: 10.1111/j.1526-4610.2011.01859.x. PMID: 21457241.

How Do We Sleep? (Neurotransmitters)

Orexin

- Dopamine
- Norepinephrine
- Serotonin**
- Histamine**

Wake Promoting

Process "S"

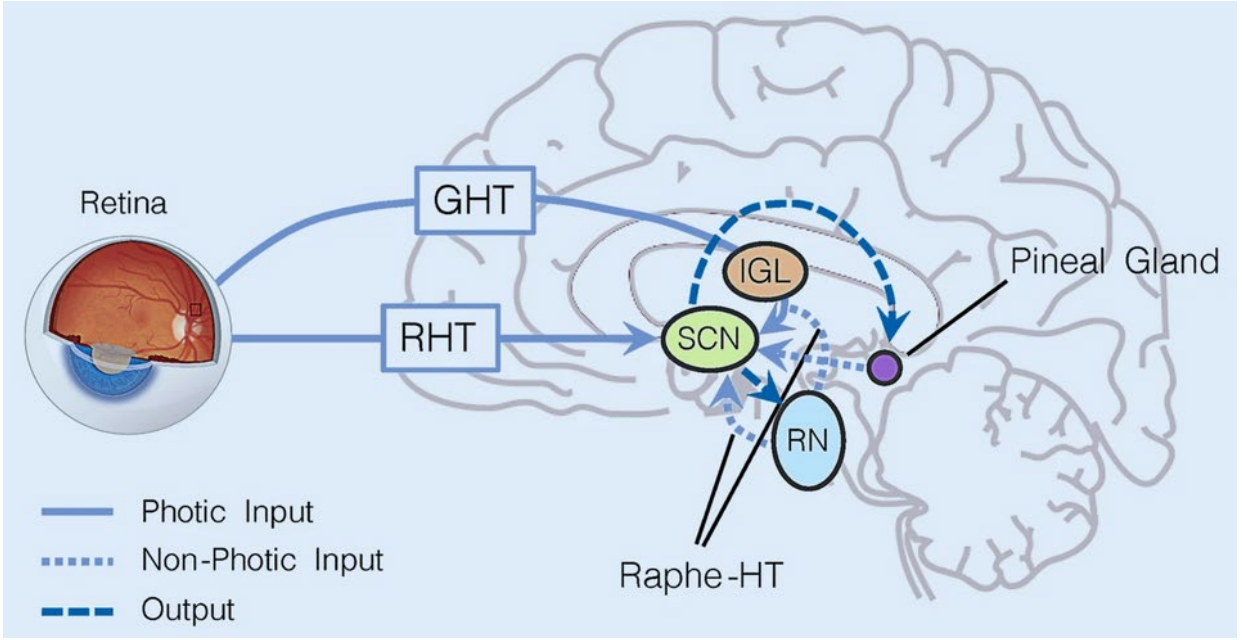
Adenosine

- GABA
- Galanin

Sleep Promoting

How Do We Sleep: Circadian Rhythms

- Feedback molecular clock (in all cells) but most importantly in the suprachiasmatic nucleus (SCN) of the hypothalamus
- Utilizes light to entrain this cycle via the retino-hypothalamic tract
- Melatonin is the main neuropeptide



Castillo PR. Clinical Neurobiology of Sleep and Wakefulness. Continuum (Minneap Minn). 2023 Aug 1;29(4):1016-1030. doi: 10.1212/CON.0000000000001260. PMID: 37590820. https://commons.wikimedia.org/wiki/File:Input_and_output_pathways_of_the_suprachiasmatic_nuclei_%28SCN%29.png

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Case 1: AM

- 45-year-old right-handed female with a history of episodic migraine
- She has 7-8 days of headache a month and is being treated with sumatriptan as needed and started on propranolol BID as she also was recently diagnosed with hypertension
- In follow up she states that she is always tired and she has very poor sleep

How to Take a Sleep History?

- When do you go to bed?
- How long does it take you to fall asleep?
- How often do you wake up
  - (and if known, what cause?)
- When do you wake up to start your day?
- Do you take naps during the day?

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Epworth Sleepiness Scale

Situation	Chance of Dozing
Sitting and reading	•
Watching TV	•
Sitting inactive in a public place (e.g., a theater or a meeting)	•
As a passenger in a car for an hour without a break	•
Lying down to rest in the afternoon when circumstances permit	•
Sitting and talking to someone	•
Sitting quietly after a lunch without alcohol	•
In a car, while stopped for a few minutes in traffic	•

Total Score = _____

- Each scenario scored from 0-3
- Based on the last 2 weeks

- 0–10: Normal daytime sleepiness
- 11–14: Mild daytime sleepiness
- 15–17: Moderate daytime sleepiness
- 18–24: Severe daytime sleepiness

- >11 warrants additional testing or query

Gonçalves MT, Malafaia S, Moutinho Dos Santos J, Roth T, Marques DR. Epworth sleepiness scale: A meta-analytic study on the internal consistency. Sleep Med. 2023 Sep;109:261-269. doi: 10.1016/j.sleep.2023.07.008. Epub 2023 Jul 17. PMID: 37487279.

Follow Up Questions?

- Sleep apnea risk factors
  - Snoring? Apneic events?
  - STOP or STOP-BANG questionnaire
- Restless leg symptoms?
- Dreams?
- Witnessed Behaviours? Injuries?

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Case: AM

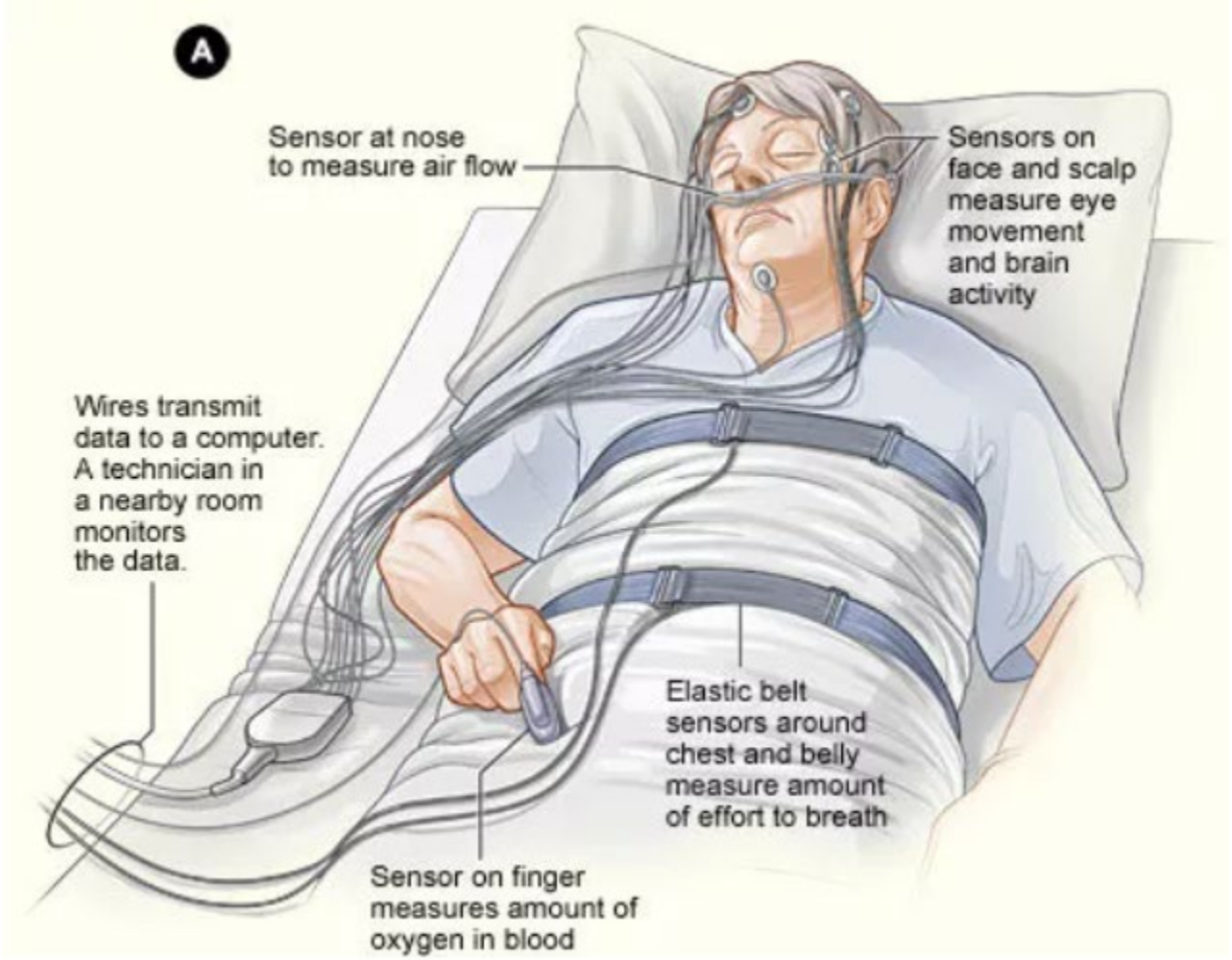
“Its always taken me forever to fall asleep. I would bet it takes me at least 45 minutes every night”

“I wake up once or twice to use the restroom and again it takes me 30 – 40 minutes to fall asleep again”

“I’m exhausted throughout the day. I don’t nap but if I had time, I probably would”

“I do not think I snore”

Polysomnography



- Electroencephalogram
- Electro-oculogram
- Electromyogram
- Electrocardiogram
- Pulse oximetry
- Airflow and respiratory effort
- Actigraphy

Rundo JV, Downey R 3rd. Polysomnography. Handb Clin Neurol. 2019;160:381-392. doi: 10.1016/B978-0-444-64032-1.00025-4. PMID: 31277862.
Addison R. Nocturia, nocturnal polyuria and secondary nocturnal voiding. Br J Nurs. 1999 Jul 8-21;8(13):877-80. doi: 10.12968/bjon.1999.8.13.6561. PMID: 10670311.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Insomnia

- Prevalence depends on the study used but ranges anywhere from one to two thirds of adults
- 10-15% of adults carry a chronic insomnia diagnosis by ICSD criterion

Table 1. *ICD-11* Diagnostic Criteria for Chronic Insomnia[a]

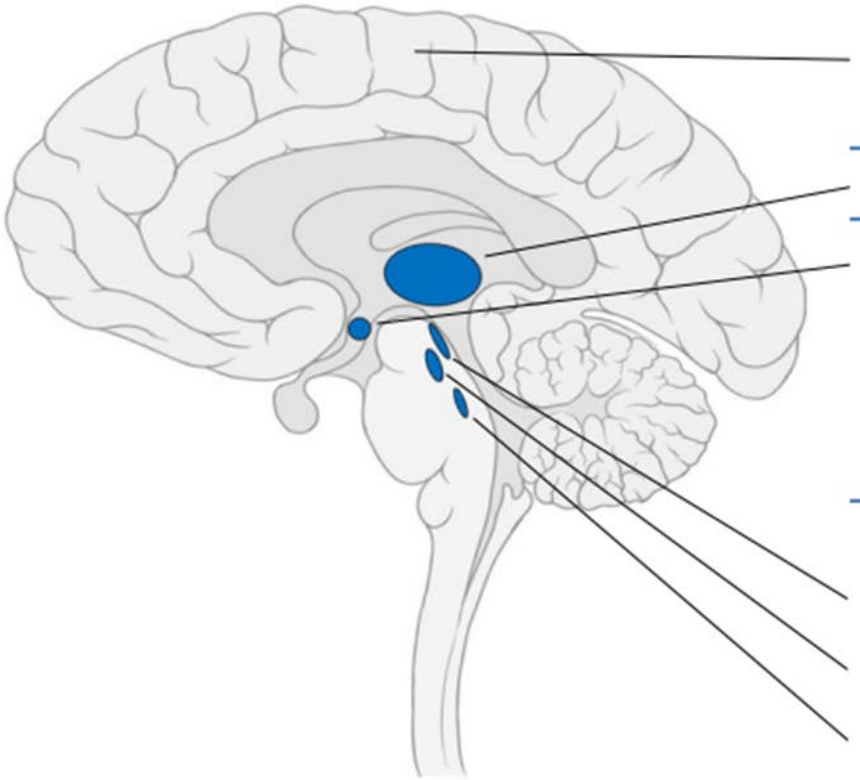
Frequent and persistent difficulty initiating or maintaining sleep
Daytime symptoms typically including fatigue, depressed mood, irritability, general malaise, and cognitive impairment
Sleep disturbance and daytime symptoms that occur at least several times per week for at least 3 months
Some individuals with chronic insomnia may show a more episodic course, with recurrent episodes of sleep/wake difficulties lasting several weeks at a time over several years
Adequate opportunity and circumstances for sleep
Daytime impairment must be present
If the insomnia is due to another sleep-wake disorder, a mental disorder, another medical condition, or a substance or medication, chronic insomnia should be diagnosed only if the insomnia is an independent focus of clinical attention

[a]From the World Health Organization. *International Classification of Diseases*, 11th Revision. 2022 release.[1]

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Odegård SS, Sand T, Engstrøm M, Stovner LJ, Zwart JA, Hagen K. The long-term effect of insomnia on primary headaches: a prospective population-based cohort study (HUNT-2 and HUNT-3). Headache. 2011 Apr;51(4):570-80. doi: 10.1111/j.1526-4610.2011.01859.x. PMID: 21457241.

Sleep Neuroanatomy

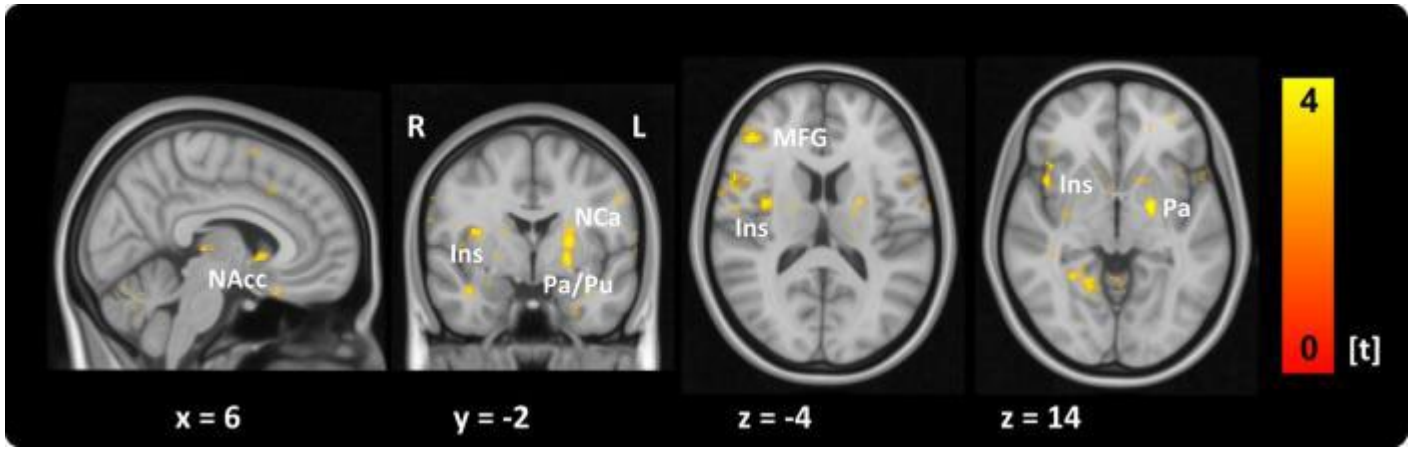


SHARED ANATOMICAL STRUCTURES	MIGRAINE	SLEEP
CORTEX	**Pain processing**: ascending thalamo-cortical projections synapse on a diffuse network of cortical regions including the primary and secondary motor somatosensory and visual cortex for pain processing **Pain modulation**: modulation of pain through descending direct and indirect projections from the cortex to the TCC	**Promotion of wakefulness** through ascending inputs from monoaminergic neurons, hypothalamus, and basal forebrain
THALAMUS	**Processing and transmission of nociceptive information** from the TCC	**Promotion of wakefulness and integration of sub-cortical sleep-wake inputs**
HYPOTHALAMUS	**Processing, transmission, and modulation of pain** from ascending pathway from the brainstem nuclei and the TCC	**Promotion of wakefulness, regulation of circadian rhythm and control of sleep-wake transition**
Posterior hypothalamus (dopamine)	The dopaminergic A11 nucleus is responsible for premonitory migraine symptoms	**Promotion of wakefulness** through the activation of the brainstem monoaminergic system, the basal forebrain, and the cortex
Lateral hypothalamus (orexin)	Orexinergic neurons facilitate or inhibit TCC nociception by receptor-specific pathway	**Control of sleep-wake transition:** participate to the "flip-flop" system for sleep-wake transition*, maintain the stability of the waking state, and prevent the inappropriate sudden onset of sleep
BRAINSTEM	**Pain transmission** from afferent fibers of TCC to the thalamus **Pain modulation** through descending inputs from thalamus and hypothalamus	**Promotion of wakefulness:** ascending activating pathways projecting from the brainstem to the thalamus and basal forebrain **Stabilization of the waking state:** receive the orexinergic excitatory projections and sends inhibitory inputs to the sleep promoting VLPO to reinforce wakefulness **Control of the transition to sleep:** inhibition of these nuclei by the VLPO promotes sleep. Noradrenergic and serotoninergic neurons inhibit the REM sleep
Periaqueductal gray (dopamine)		
Dorsal raphe nucleus (serotonin)		
Locus coeruleus (norepinephrine)		

Odegård SS, Sand T, Engstrøm M, Stovner LJ, Zwart JA, Hagen K. The long-term effect of insomnia on primary headaches: a prospective population-based cohort study (HUNT-2 and HUNT-3). Headache. 2011 Apr;51(4):570-80. doi: 10.1111/j.1526-4610.2011.01859.x. PMID: 21457241.

Hypothalamus and Migraine

- Critical structure implicated in both sleep and migraine with multiple studies and of interest in prodromal/preictal phenomenon
- A 2021 longitudinal MRI study observed the functional connectivity between the hypothalamus and other limbic centres increasing linearly over the interictal interval, reaching its peak shortly before a headache is initiated



Stankewitz A, Keidel L, Rehm M, Irving S, Kaczmarz S, Preibisch C, Witkovsky V, Zimmer C, Schulz E, Toelle TR. Migraine attacks as a result of hypothalamic loss of control. Neuroimage Clin. 2021;32:102784. doi: 10.1016/j.nicl.2021.102784. Epub 2021 Aug 16. PMID: 34425551; PMCID: PMC8379646.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Migraine and Insomnia

- Patients diagnosed with insomnia had a higher risk of developing migraine (in the next 11 years)
- Patients with migraine had a 2-fold risk to develop insomnia, higher in those with at least 7 days of headache per month
- Insomnia was also correlated with higher perceived migraine intensity, functional impact, attack frequency and rates of chronicification of migraine not solely attributable to other factors such as anxiety or depression

Tiseo C, Vacca A, Felbush A, Filimonova T, Gai A, Glazyrina T, Hubalek IA, Marchenko Y, Overeem LH, Piroso S, Tkachev A, Martelletti P, Sacco S; European Headache Federation School of Advanced Studies (EHF-SAS). Migraine and sleep disorders: a systematic review. J Headache Pain. 2020 Oct 27;21(1):126. doi: 10.1186/s10194-020-01192-5. PMID: 33109076; PMCID: PMC7590682.

Interictal Sleep Quality in Migraine

- Adults with migraine consistently report poorer sleep quality compared to controls as per PSQI scores
- On polysomnography:
  - A modestly lower percentage of REM sleep in those with migraine
  - Shorter sleep duration has been associated with increased migraine frequency

Vgontzas A, Pavlović J, Bertisch S. Sleep Symptoms and Disorders in Episodic Migraine: Assessment and Management. Curr Pain Headache Rep. 2023 Oct;27(10):511-520. doi: 10.1007/s11916-023-01160-z. Epub 2023 Sep 4. PMID: 37665530.
Stanyer EC, Hoffmann J, Holland PR. Orexins and primary headaches: an overview of the neurobiology and clinical impact. Expert Rev Neurother. 2024 May;24(5):487-496. doi: 10.1080/14737175.2024.2328728. Epub 2024 Mar 22. PMID: 38517280; PMCID: PMC11034548.

Migraine and Insomnia

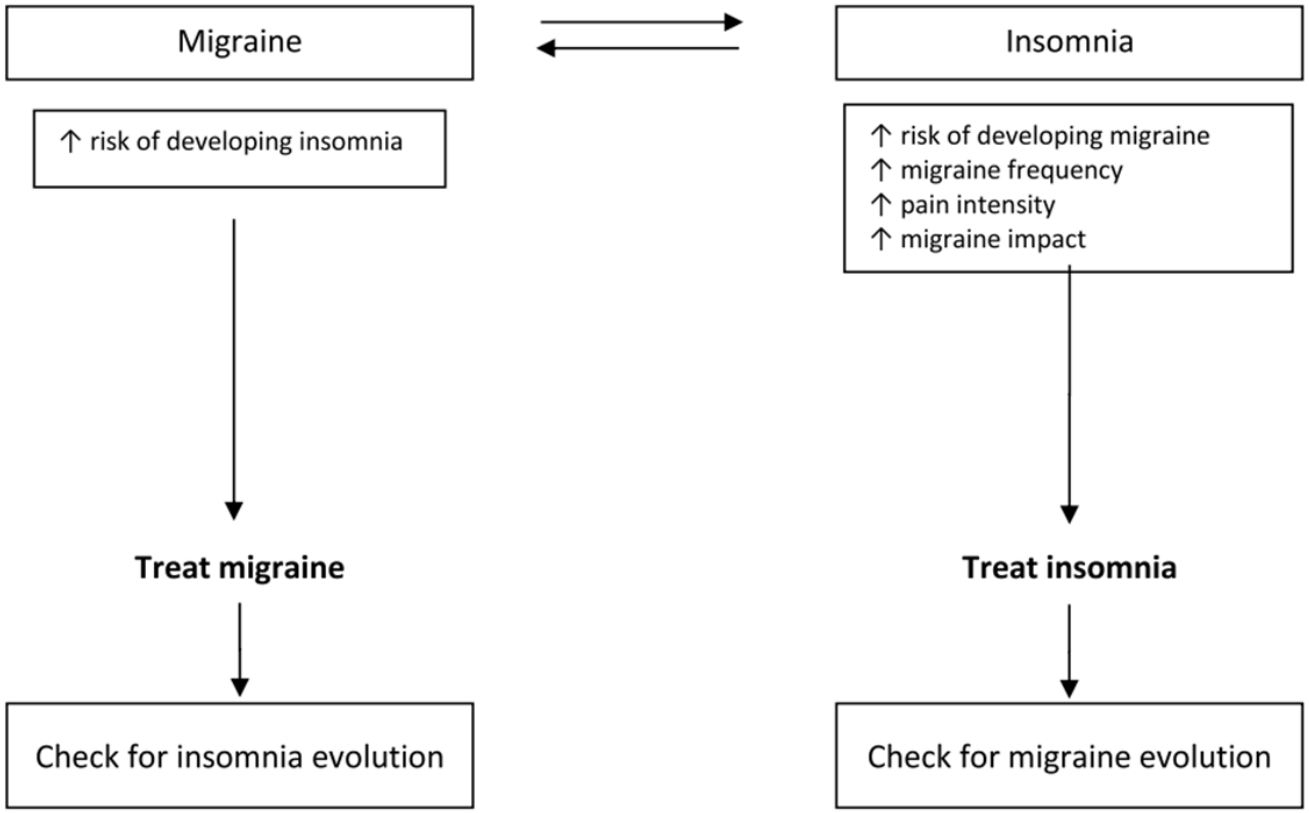
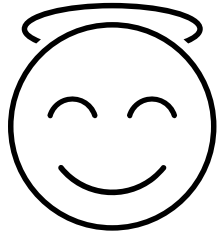


Fig. 2 Interaction between migraine and insomnia. Available evidence suggests the existence of a bidirectional association between migraine and insomnia that is independent from anxiety and depression. Migraine patients are at increased risk of developing insomnia, and insomnia is a risk factor for migraine onset and for increased migraine impact, pain intensity, and chronification. Routine evaluation of the presence of insomnia complaints in patients with migraine and implementation of specific pharmacological and non-pharmacological insomnia treatments would be appropriate since a reduction of migraine burden might be observed

Odegård SS, Sand T, Engstrøm M, Stovner LJ, Zwart JA, Hagen K. The long-term effect of insomnia on primary headaches: a prospective population-based cohort study (HUNT-2 and HUNT-3). Headache. 2011 Apr;51(4):570-80. doi: 10.1111/j.1526-4610.2011.01859.x. PMID: 21457241.

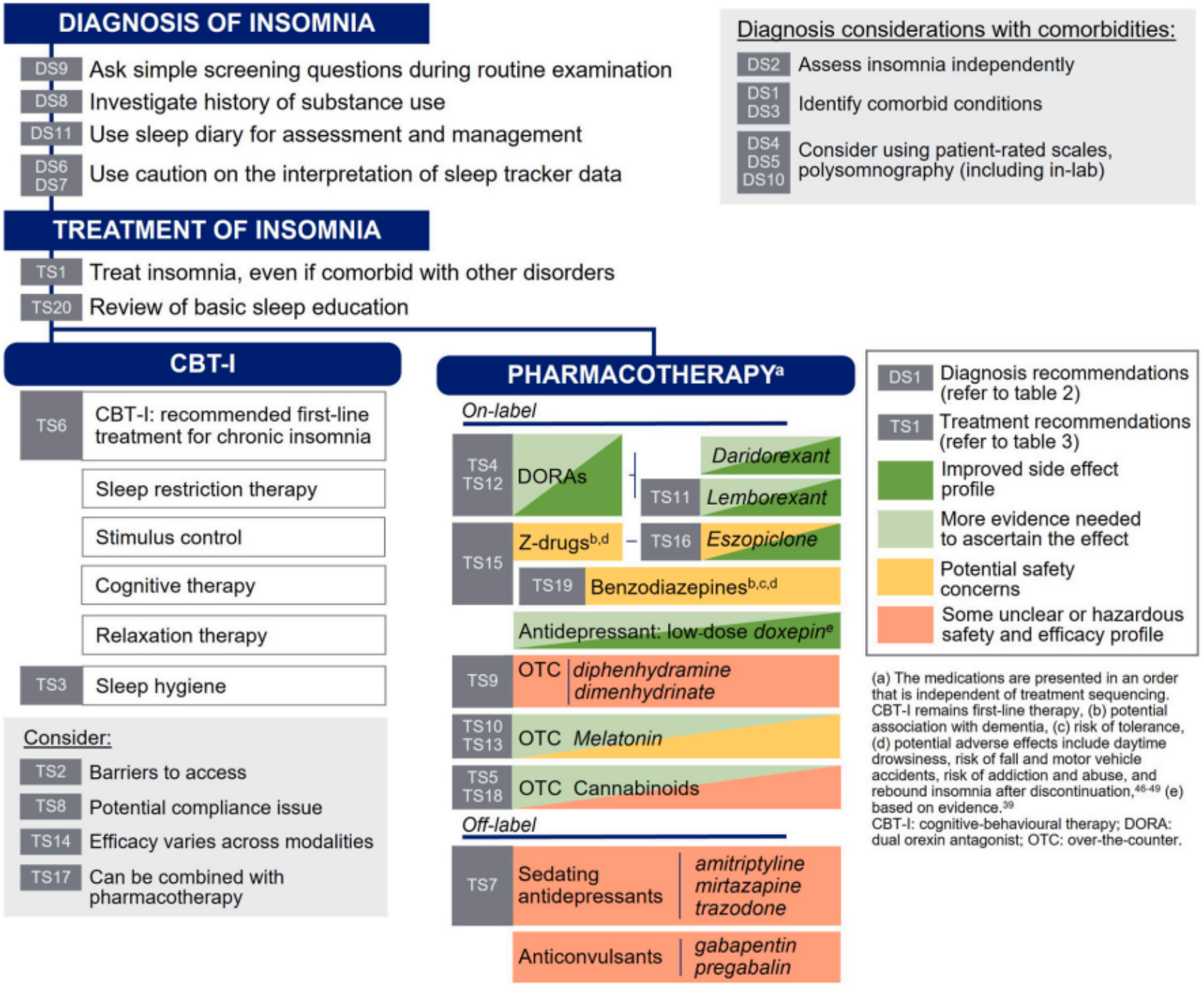
Migraine and Insomnia

- A prospective diary and actigraphy study which examined multidimensional sleep health among adults with episodic migraine found that those with better sleep health had 3–4 less headache days per month on average



Vgontzas A, Pavlović J, Bertisch S. Sleep Symptoms and Disorders in Episodic Migraine: Assessment and Management. Curr Pain Headache Rep. 2023 Oct;27(10):511-520. doi: 10.1007/s11916-023-01160-z. Epub 2023 Sep 4. PMID: 37665530.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST



(a) The medications are presented in an order that is independent of treatment sequencing. CBT-I remains first-line therapy, (b) potential association with dementia, (c) risk of tolerance, (d) potential adverse effects include daytime drowsiness, risk of fall and motor vehicle accidents, risk of addiction and abuse, and rebound insomnia after discontinuation,[46-49] (e) based on evidence.[39]
CBT-I: cognitive-behavioural therapy; DORA: dual orexin antagonist; OTC: over-the-counter.

Morin CM, Khullar A, Robillard R, Desautels A, Mak MSB, Dang-Vu TT, Chow W, Habert J, Lessard S, Alima L, Ayas NT, MacFarlane J, Kendzerska T, Lee EK, Carney CE. Delphi consensus recommendations for the management of chronic insomnia in Canada. Sleep Med. 2024 Dec;124:598-605. doi: 10.1016/j.sleep.2024.09.038. Epub 2024 Oct 5. PMID: 39481275.

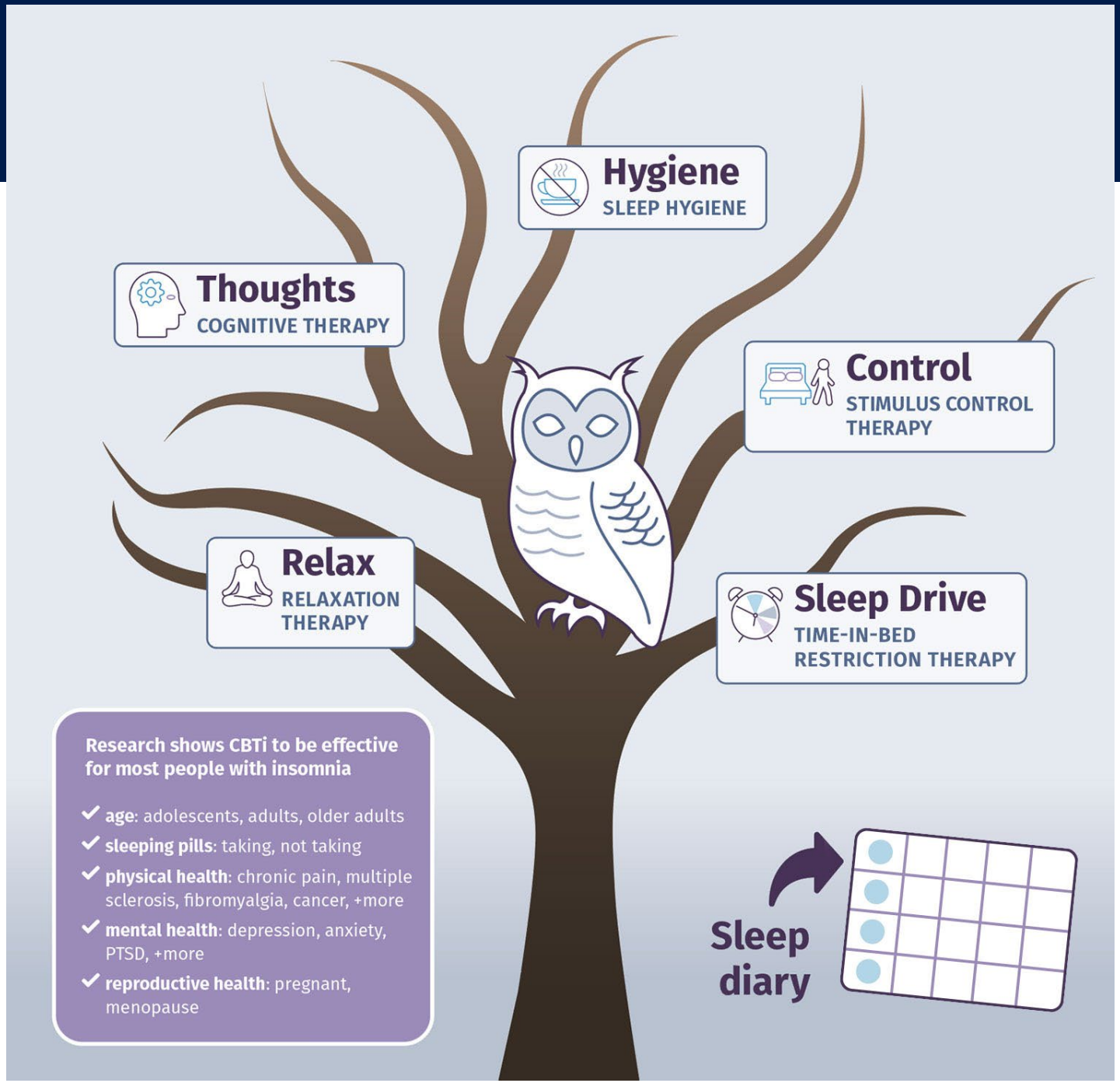
CANADIAN HEADACHE CONFERENCE COAST TO COAST

‘Sleep Hygiene’

- Maintain a cool environment
- No caffeine 6 hours before intended sleep time
- No alcohol directly before intended sleep time
- No exercise directly before intended sleep time
- Optimize sleep environment: no noises, no screens or bright lighting before intended sleep time, attempt to separate sleep from workspace
- Optimize water consumption and voiding where possible

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

CBTi



https://mysleepwell.ca/

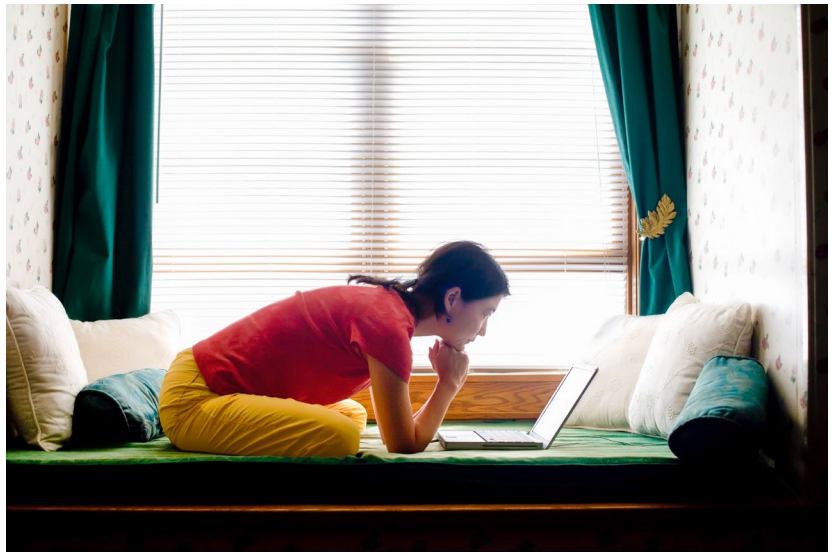
CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Stimulus Control Therapy

Core Principle of CBTi

5 Rules:

1. Wake up at the same time every day
2. Only attempt to sleep when sleepy
3. “10 to15-minute rule”
4. Bed is only for sleep
5. No naps



CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Case: AM

“Doc, I swear that every time I have a bad night of sleep, the next day I have a migraine. I can’t remember getting a headache without that.”

“Lack of sleep is a known trigger, right?

“If I fix my sleep, my migraine will be cured, right??”

Sleep Disruption as a Migraine Trigger

- Retrospective studies report that sleep changes are among the most commonly reported migraine triggers
- Changes to the light–dark cycle, such as jet lag and shift-work are commonly reported as triggers for attacks

J Headache Pain. 2020 Jul 6;21(1):86. doi: 10.1186/s10194-020-01155-w

Acute sleep deprivation enhances susceptibility to the migraine substrate cortical spreading depolarization

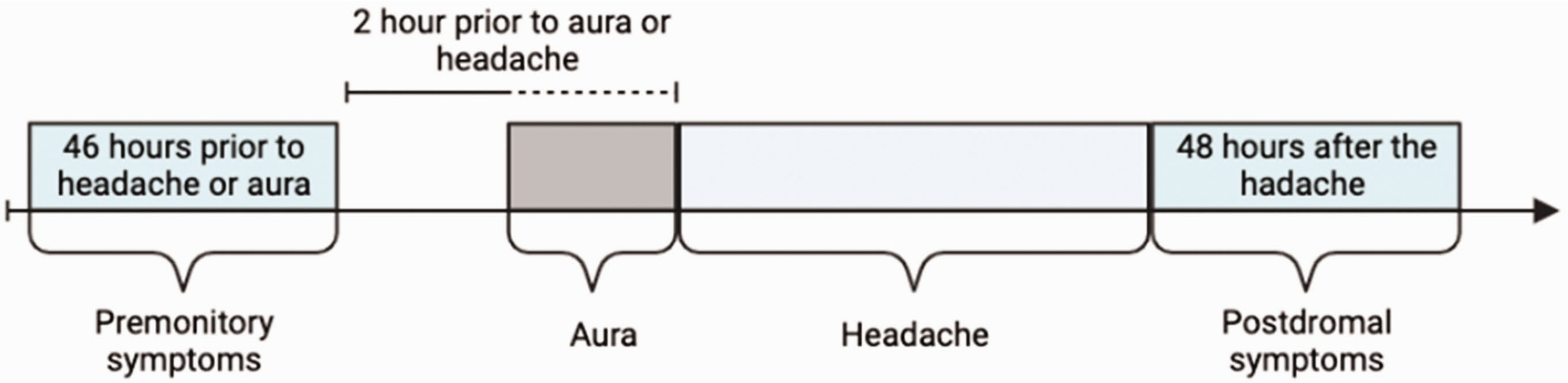
Andrea Negro [1,2], Jessica L Seidel [1], Thijs Houben [1], Esther S Yu [1], Ike Rosen [1], Andrea J Arreguin [1], Nilufer Yalcin [1], Lea Shorser-Gentile [1], Lea Pearlman [1], Homa Sadhegian [1], Ramalingam Vetrivelan [3], Nancy L Chamberlin [4], Cenk Ayata [1,5], Paolo Martelletti [2], Michael A Moskowitz [6], Katharina Eikermann-Haerter [1,7]✉

Author information · Article notes · Copyright and License information

PMCID: PMC7339460 PMID: 32631251

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Migraine Prodrome



Thuraiaiyah J, Ashina H, Christensen RH, et al. Premonitory symptoms in migraine: A REFORM Study. *Cephalalgia*. 2024;44(2).

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Migraine Prodrome

Common symptoms experienced during this phase include:

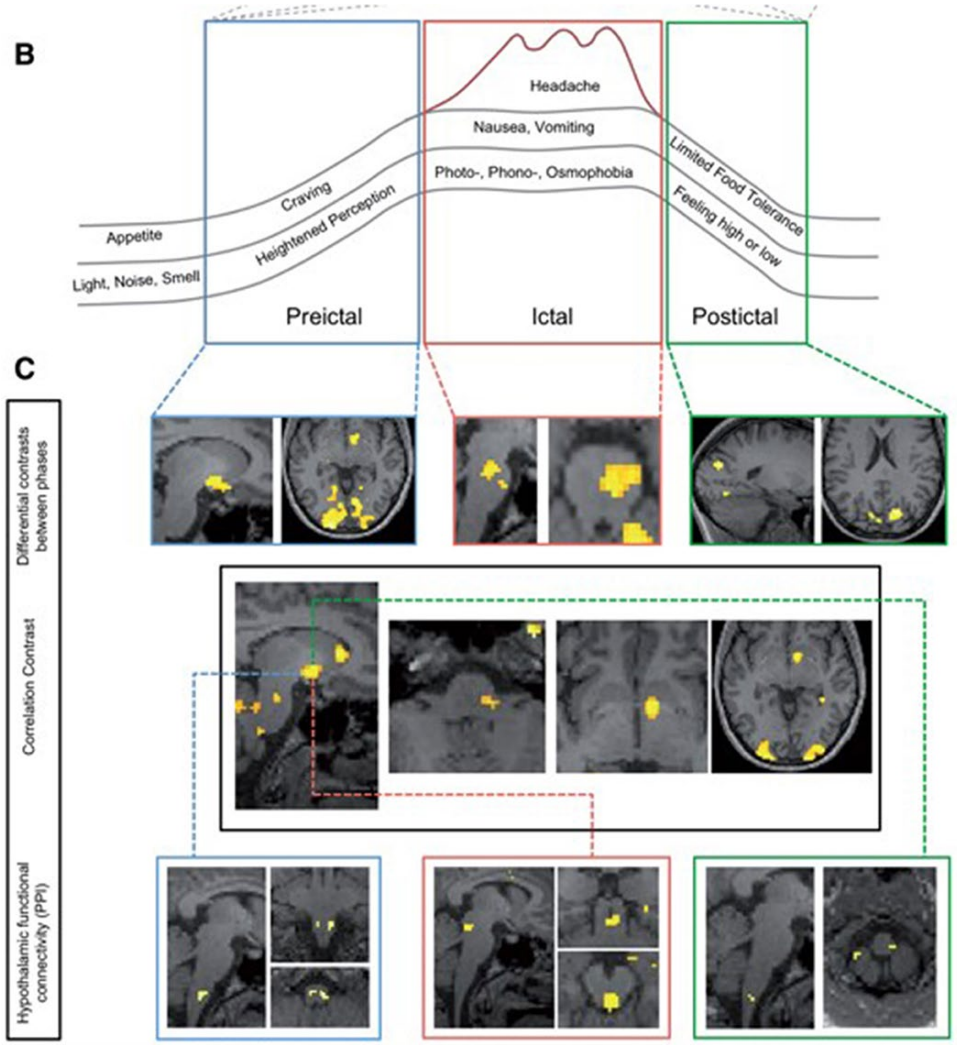
- Fatigue
- Mood Changes
- Food Cravings
- Yawning
- Muscle Tenderness
- Photophobia

This suggests involvement of the hypothalamus, brainstem, limbic system, and certain cortical areas during the early stages of an attack

Dodick DW. A Phase-by-Phase Review of Migraine Pathophysiology. Headache. 2018 May;58 Suppl 1:4-16. doi: 10.1111/head.13300. PMID: 29697154.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Hypothalamus and Migraine Prodrome



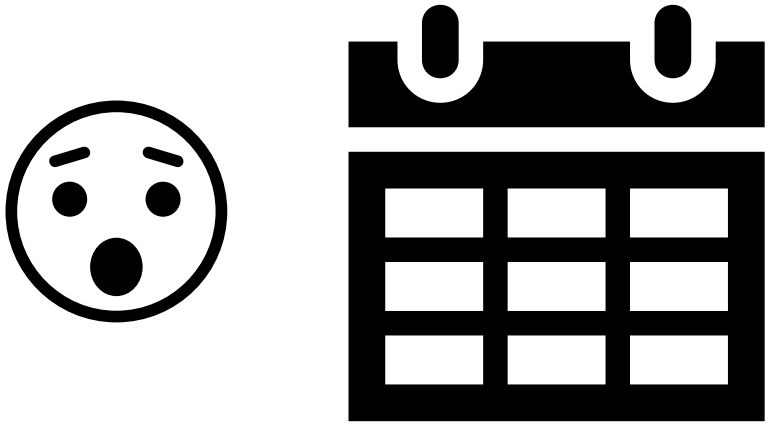
- Migraine-associated prodromal symptoms involving mood changes, fatigue, food cravings are likely processed by hypothalamic areas
- Alterations in hypothalamic functional connectivity shortly before the beginning of migraine headaches could indicate a predominant role in migraine attack generation

May A, Burstein R. Hypothalamic regulation of headache and migraine. Cephalalgia. 2019 Nov;39(13):1710-1719. doi: 10.1177/0333102419867280. Epub 2019 Aug 29. PMID: 31466456; PMCID: PMC7164212.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Sleep Quality in the Migraine Prodrome

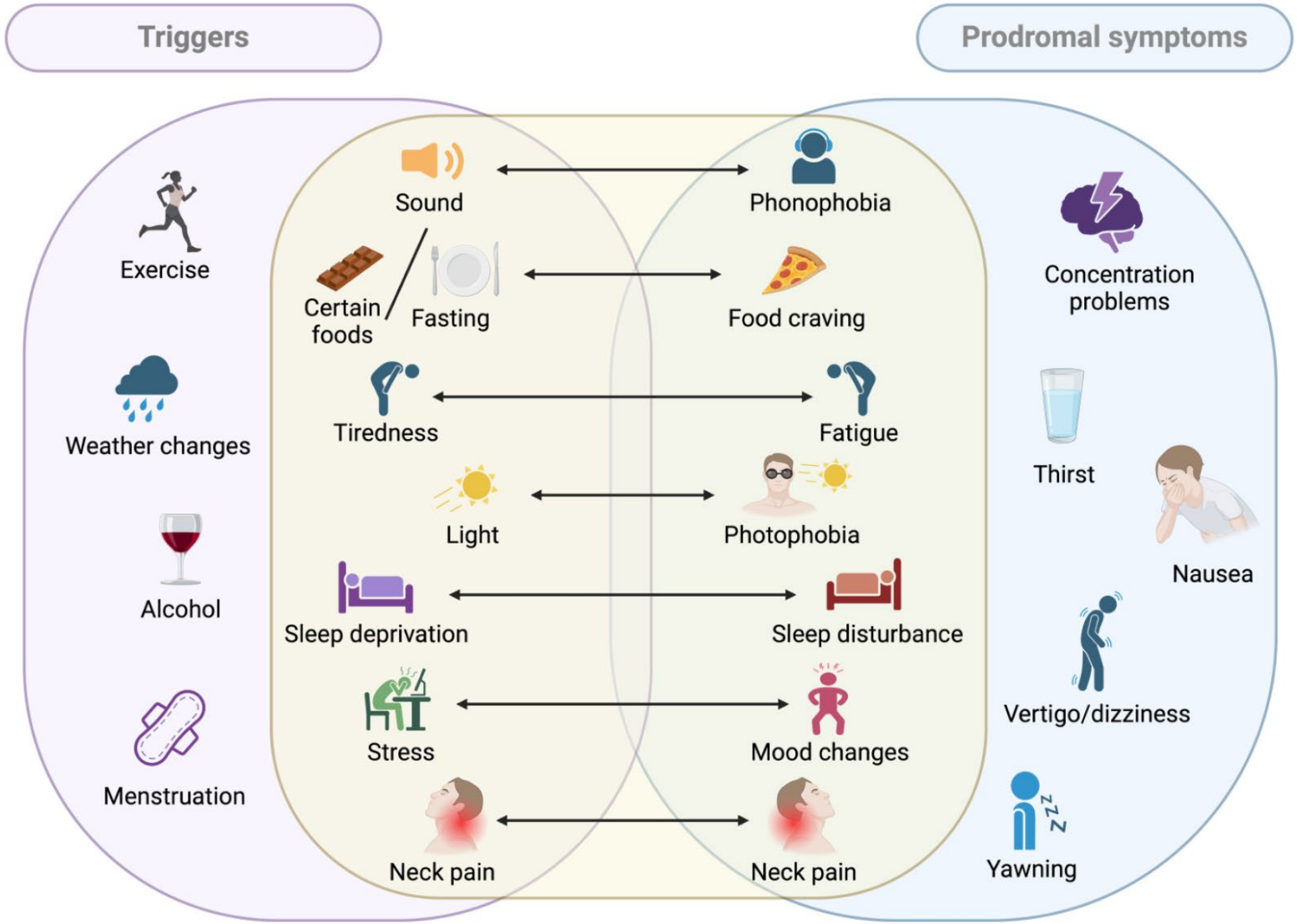
A 6-week actigraphy study in one-hundred adults with episodic migraine did not find differences in sleep duration, quality, and sleep latency the night before a migraine attack, but did report lower sleep efficiency **two nights** prior to a migraine attack



Vgontzas A, Li W, Mostofsky E, Rueschman M, Mittleman MA, Bertisch SM. Associations between migraine attacks and nightly sleep characteristics among adults with episodic migraine: a prospective cohort study. Sleep. 2020 Jul 13;43(7):zsaa001.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Prodrome vs Triggers



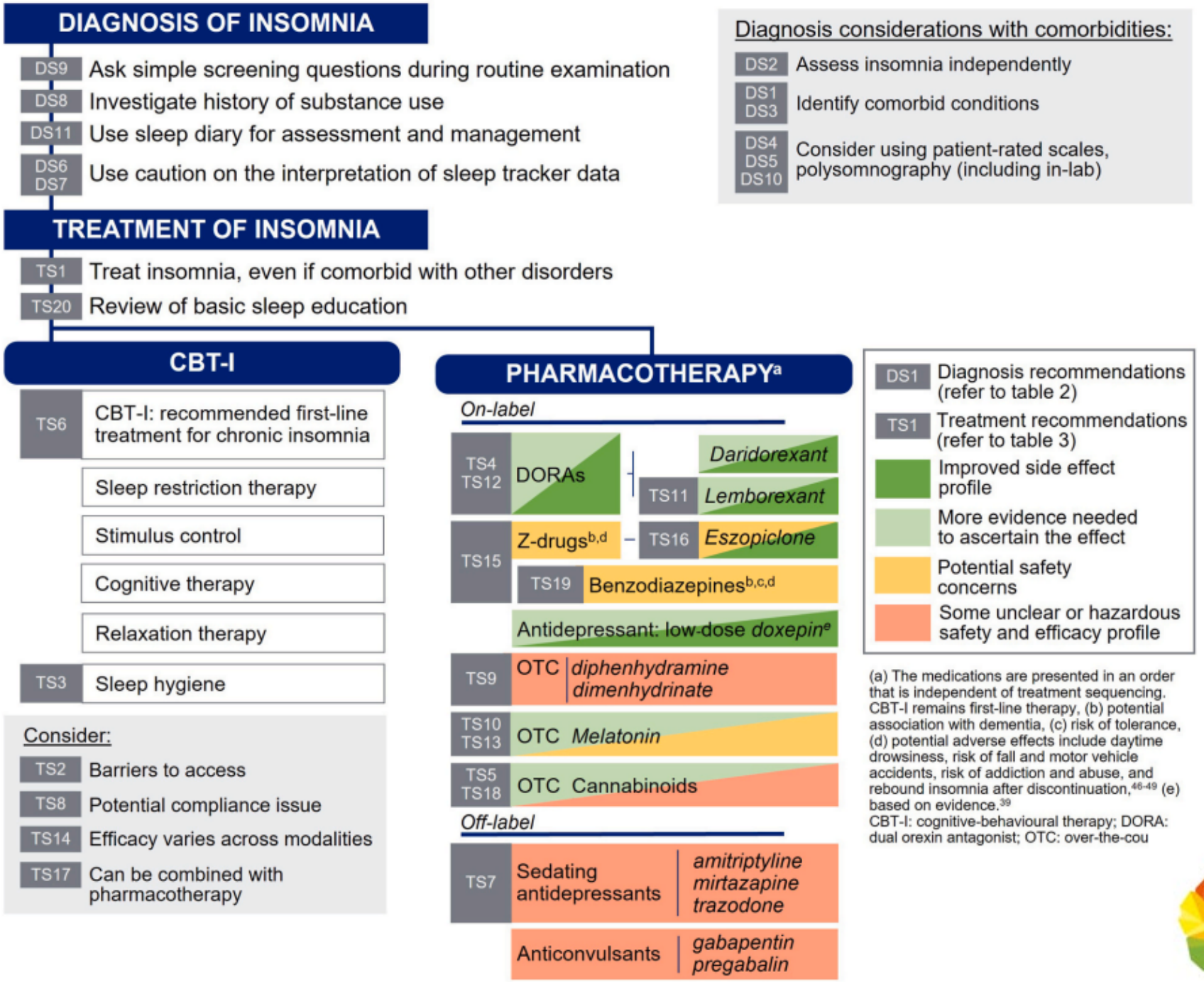
Sebastianelli G, Atalar AÇ, Cetta I, Farham F, Fitzek M, Karatas-Kursun H, Kholodova M, Kukumägi KH, Montisano DA, Onan D, Pantovic A, Skarlet J, Sotnikov D, Caronna E, Pozo-Rosich P; International Headache Academy of the International Headache Society (IHS-iHEAD). Insights from triggers and prodromal symptoms on how migraine attacks start: The threshold hypothesis. Cephalalgia.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Case: AM

“I STILL can’t sleep, I swear I’m trying to do everything you say but there are so many things going on!”

“Is there anything else you can do??”



(a) The medications are presented in an order that is independent of treatment sequencing. CBT-I remains first-line therapy, (b) potential association with dementia, (c) risk of tolerance, (d) potential adverse effects include daytime drowsiness, risk of fall and motor vehicle accidents, risk of addiction and abuse, and rebound insomnia after discontinuation,[46-49] (e) based on evidence.[39]
CBT-I: cognitive-behavioural therapy; DORA: dual orexin antagonist; OTC: over-the-cou

Morin CM, Khullar A, Robillard R, Desautels A, Mak MSB, Dang-Vu TT, Chow W, Habert J, Lessard S, Alima L, Ayas NT, MacFarlane J, Kendzerska T, Lee EK, Carney CE. Delphi consensus recommendations for the management of chronic insomnia in Canada. Sleep Med. 2024 Dec;124:598-605. doi: 10.1016/j.sleep.2024.09.038. Epub 2024 Oct 5. PMID: 39481275.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

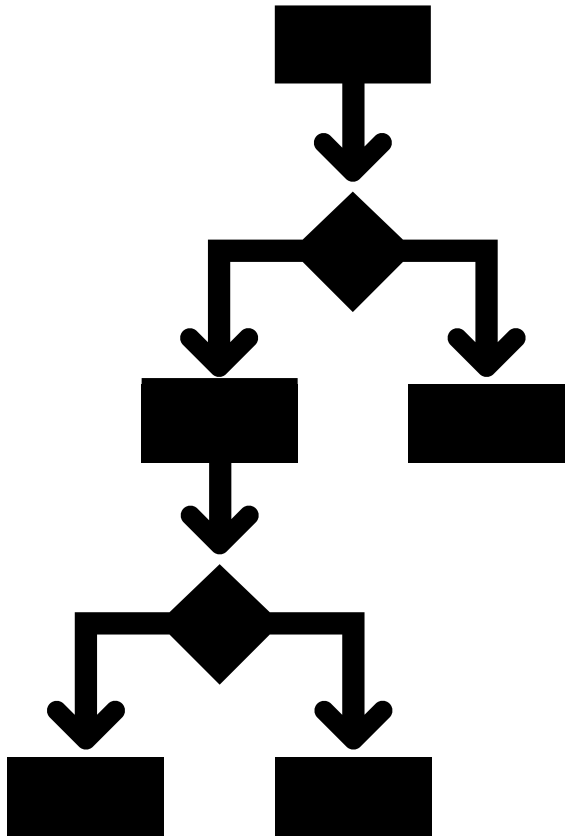
Second Line Sleep Therapy

General overtures of sleep therapy are:

- Increase the sleep signal
- Decrease the arousal signal

Practical Tips:

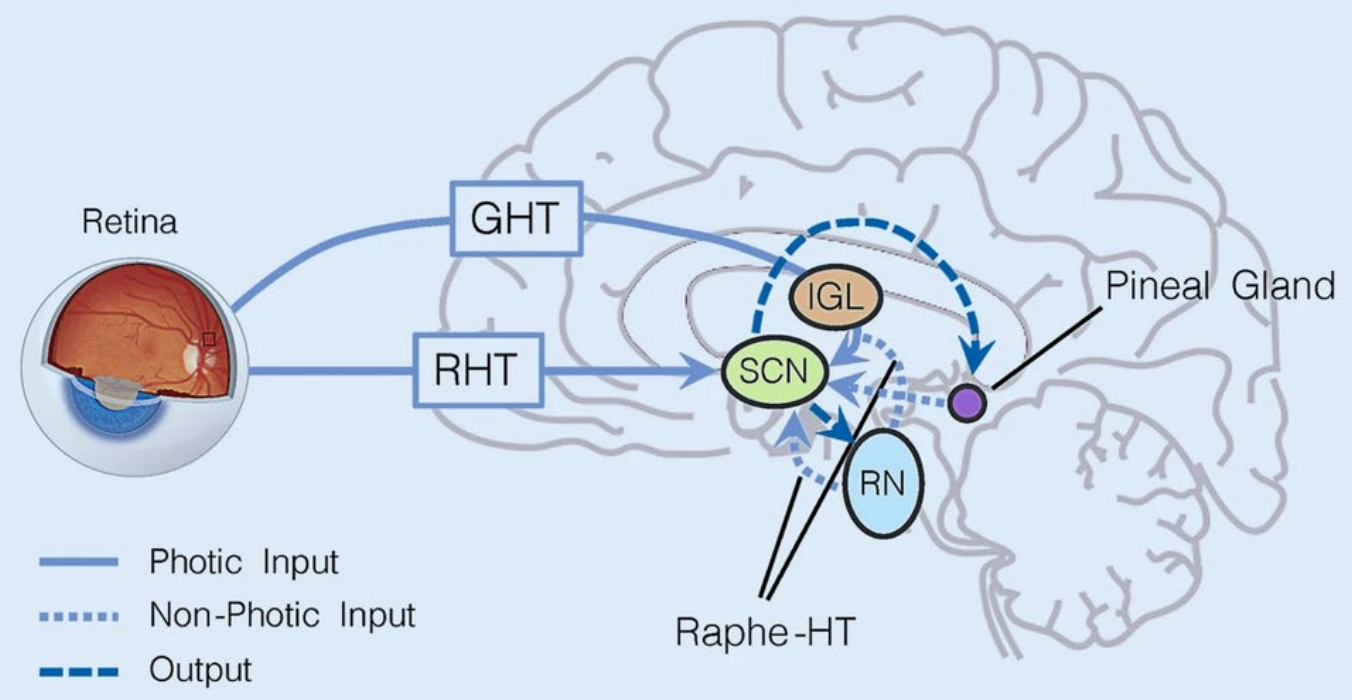
- CHOOSE AN AGENT WISELY
- ALWAYS HAVE AN EXIT STRATEGY



CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Melatonin

Poor hypnotic, primary benefit in phase shift and circadian correction



Nelakuditi B, Dandamudi BJ, Dimaano KAM, Shah N, AlQassab O, Al-Sulaitti Z, Khan S. Efficacy of Melatonin as a Promising Intervention for Migraine Prevention: A Systematic Review of Randomized Control Trials. Cureus. 2024 Oct 28;16(10):e72559. doi: 10.7759/cureus.72559. PMID: 39606511; PMCID: PMC11601882.
https://commons.wikimedia.org/wiki/File:Input_and_output_pathways_of_the_suprachiasmatic_nuclei_%28SCN%29.png

Melatonin and Migraine

- A 2024 systematic review of seven randomized control trials involving 1,283 migraine patients were treated with melatonin or agomelatine compared to those treated with conventional prophylactic therapy or placebo
- The findings of this review suggested that melatonin could significantly reduces the frequency and severity of migraines, but its dose-dependent action and benefits remain debatable

Nelakuditi B, Dandamudi BJ, Dimaano KAM, Shah N, AlQassab O, Al-Sulaitti Z, Khan S. Efficacy of Melatonin as a Promising Intervention for Migraine Prevention: A Systematic Review of Randomized Control Trials. Cureus. 2024 Oct 28;16(10):e72559. doi: 10.7759/cureus.72559. PMID: 39606511; PMCID: PMC11601882.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Why Isn't it Working?

- Melatonin content was found to range from -83% to +478% of the labelled content. Additionally, lot-to-lot variable within a particular product varied by as much as 465%
- Melatonin content did not meet label within a 10% margin of the label claim in more than 71% of supplements and an additional 26% were found to contain serotonin

J Clin Sleep Med. 2017 Feb 15;13(2):275-281. doi: 10.5664/jcsm.6462.

Melatonin Natural Health Products and Supplements: Presence of Serotonin and Significant Variability of Melatonin Content

Lauren A E Erland [1], Praveen K Saxena [1]

Affiliations + expand

PMID: 27855744 PMCID: PMC5263083 DOI: 10.5664/jcsm.6462

Abstract

Study objectives: Melatonin is an important neurohormone, which mediates circadian rhythms and the sleep cycle. As such, it is a popular and readily available supplement for the treatment and prevention of sleep-related disorders including insomnia and jet lag. This study quantified melatonin in 30 commercial supplements, comprising different brands and forms and screened supplements for the presence of serotonin.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Why is it Working a Little TOO Well….

Quantity of Melatonin and CBD in Melatonin Gummies Sold in the US

Pieter A Cohen [1], Bharathi Avula [2], Yan-Hong Wang [2], Kumar Katragunta [2], Ikhlas Khan [2]

Affiliations + expand

PMID: 37097362 PMCID: PMC10130950 DOI: 10.1001/jama.2023.2296

Results

Of the 30 melatonin gummy brands meeting the inclusion criteria, 4 were unavailable for purchase and 1 did not contain "melatonin" on the actual label; therefore, 25 products were analyzed. One product did not contain detectable levels of melatonin but did contain 31.3 mg of CBD. In the remaining products, the quantity of melatonin ranged from 1.3 mg to 13.1 mg per serving size (Table). In products that contained melatonin, the actual quantity of melatonin ranged from 74% to 347% of the labeled quantity. Twenty-two of 25 products (88%) were inaccurately labeled, and only 3 products (12%) contained a quantity of melatonin that was within ±10% of the declared quantity. Five products declared CBD as an ingredient, and the quantity of CBD ranged from 10.6 mg to 31.3 mg per serving. The actual quantity of CBD ranged from 104% to 118% of the labeled quantity. Serotonin was not detected in any product.

Table 2. Medications for the Treatment of Insomnia[a]

Class/Drug	Dosage (mg)[b]	Mechanism
Antidepressants		
Doxepin[c]	3–6	Serotonin-norepinephrine reuptake inhibitor; H_1 receptor blocker
Amitriptyline[d]	10–25	
Trazodone[d]	25–100	Serotonin antagonist and reuptake inhibitor; H_1 receptor blocker
Mirtazepine[d]	3.75–7.5	Serotonin-norepinephrine transmission blocker; H_1 receptor blocker
Benzodiazepines		
Alprazolam[d]	0.25–0.5	$GABA_A$-receptor agonists
Clonazepam[d]	0.25–2	
Estazolam	1–2	
Flurazepam	15–30	
Lorazepam	1–2	
Quazepam	7.5–15	
Temazepam	7.5–30	
Triazolam	0.125–0.5	
Benzodiazepine receptor agonists		
Eszopiclone[e]	1–3	$GABA_A$-receptor agonists
Zaleplon	5–20	
Zolpidem[f]	5–10	
Melatonin agonist		
Ramelteon	8	Highly selective melatonin-receptor agonist
Dual orexin receptor antagonists		
Daridorexant	25–50	Dual orexin receptor antagonists
Lemborexant	5–10	
Suvorexant	10–20	

Rosenberg RP, Benca R, Doghramji P, Roth T. A 2023 Update on Managing Insomnia in Primary Care: Insights From an Expert Consensus Group. Prim Care Companion CNS Disord. 2023 Jan 24;25(1):22nr03385. doi: 10.4088/PCC.22nr03385. PMID: 36705978.

Table 2. Medications for the Treatment of Insomnia[a]

Class/Drug	Dosage (mg)[b]	Mechanism
Antidepressants		
Doxepin[c]	3–6	Serotonin-norepinephrine reuptake inhibitor; H_1 receptor blocker
Amitriptyline[d]	10–25	
Trazodone[d]	25–100	Serotonin antagonist and reuptake inhibitor; H_1 receptor blocker
Mirtazepine[d]	3.75–7.5	Serotonin-norepinephrine transmission blocker; H_1 receptor blocker
Benzodiazepines		
Alprazolam[d]	0.25–0.5	$GABA_A$-receptor agonists
Clonazepam[d]	0.25–2	
Estazolam	1–2	
Flurazepam	15–30	
Lorazepam	1–2	
Quazepam	7.5–15	
Temazepam	7.5–30	
Triazolam	0.125–0.5	
Benzodiazepine receptor agonists		
Eszopiclone[e]	1–3	$GABA_A$-receptor agonists
Zaleplon	5–20	
Zolpidem[f]	5–10	
Melatonin agonist		
Ramelteon	8	Highly selective melatonin-receptor agonist
Dual orexin receptor antagonists		
Daridorexant	25–50	Dual orexin receptor antagonists
Lemborexant	5–10	
Suvorexant	10–20	

Rosenberg RP, Benca R, Doghramji P, Roth T. A 2023 Update on Managing Insomnia in Primary Care: Insights From an Expert Consensus Group. Prim Care Companion CNS Disord. 2023 Jan 24;25(1):22nr03385. doi: 10.4088/PCC.22nr03385. PMID: 36705978.

Dual Orexin Receptor Antagonists (DORAs)

Daridorexant	Orexin (hypocretin)	25 mg to 50 mg	8 h
Lemborexant	Orexin (hypocretin)	5 mg to 10 mg	17 h to 19 h
Suvorexant	Orexin (hypocretin)	5 mg to 20 mg, trials studied up to 40 mg (30 mg in people ≥65 years old)	12 h

Castillo PR. Clinical Neurobiology of Sleep and Wakefulness. Continuum (Minneap Minn). 2023 Aug 1;29(4):1016-1030. doi: 10.1212/CON.0000000000001260. PMID: 37590820.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Practical Notes on Using DORAs

Side effects:

- Most common:
  - Drowsiness
  - Headache
- Vivid dreams / nightmares
- Sleep Paralysis / Cataplexy
- Morning dizziness and fatigue (‘hangover’-like feeling)

Who should NOT use DORAs:

- Narcolepsy Type 1
- Sleep Behavioural Disorders

Rocha RB, Bomtempo FF, Nager GB, Cenci GI, Telles JPM. Dual orexin receptor antagonists for the treatment of insomnia: systematic review and network meta-analysis. Arq Neuropsiquiatr. 2023 May;81(5):475-483. doi: 10.1055/s-0043-1768667. Epub 2023 May 31. \

Orexin Blockers as Migraine Therapy?

- In preclinical models, a precursor of suvorexant, (DORA-12) demonstrated:
  - Inhibition of trigeminal nociception
  - Increased threshold for inducing cortical spreading depression
  - Attenuated neurogenically-induced vasodilation of the middle meningeal artery

Stanyer EC, Hoffmann J, Holland PR. Orexins and primary headaches: an overview of the neurobiology and clinical impact. Expert Rev Neurother. 2024 May;24(5):487-496. doi: 10.1080/14737175.2024.2328728. Epub 2024 Mar 22. PMID: 38517280; PMCID: PMC11034548

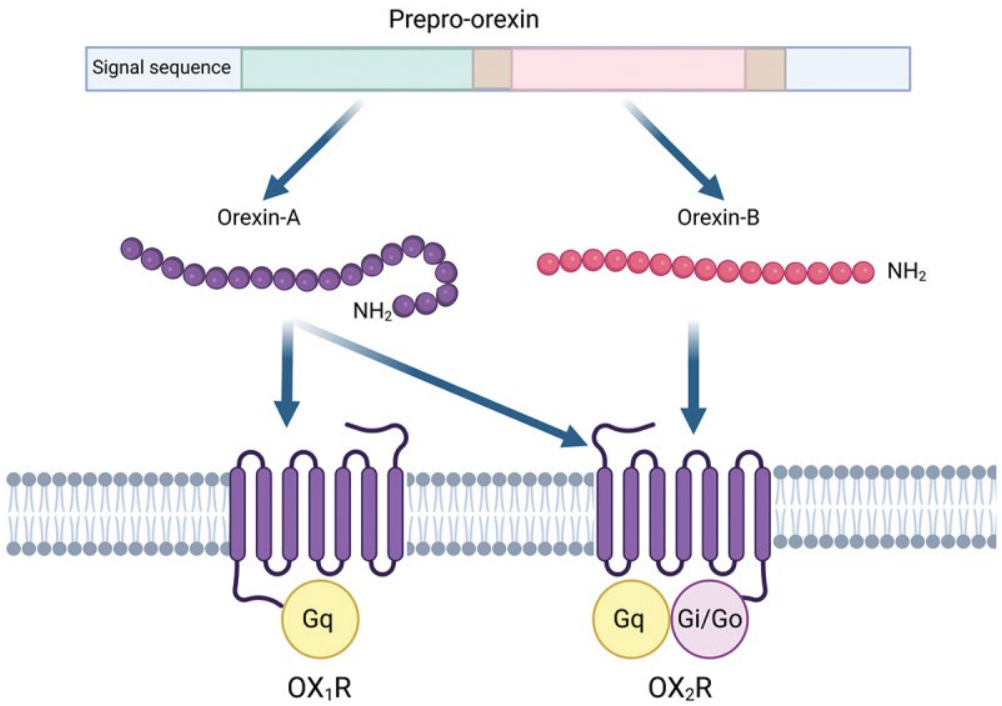
Orexin Blockers as Migraine Therapy?

- In a 2015 randomized control study of 120 patients and 115 controls treated with filorexant as prophylaxis
- There was no statistically significant difference for:
  - Change from baseline in mean monthly migraine days (filorexant = -1.7, placebo = -1.3, difference = -0.4 (95% CI: -1.3, 0.4))
  - Headache days (filorexant = -1.7, placebo = -1.2, difference = -0.5 (95% CI: -1.4, 0.4)).

Chabi A, Zhang Y, Jackson S, Cady R, Lines C, Herring WJ, Connor KM, Michelson D. Randomized controlled trial of the orexin receptor antagonist filorexant for migraine prophylaxis. Cephalalgia. 2015 Apr;35(5):379-88. doi: 10.1177/0333102414544979. Epub 2014 Aug 8. PMID: 25106663.

Sleep and Migraine: Orexin / Hypocretin

- Orexin (hypocretin) peptides have two isoforms:
- Orexin-A (ORX1 or hypocretin-1)
- Reported to have anti-nociceptive effects in the brain and spine
- Orexin-B (ORX2 or hypocretin-2)
- No anti-nociceptive effects, potentially PRO-nociceptive



Stanyer EC, Hoffmann J, Holland PR. Orexins and primary headaches: an overview of the neurobiology and clinical impact. Expert Rev Neurother. 2024 May;24(5):487-496. doi: 10.1080/14737175.2024.2328728. Epub 2024 Mar 22. PMID: 38517280; PMCID: PMC11034548

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Sleep Therapy + Migraine Therapy

Table 1 Headache preventive medications and potential influences on sleep

Category	Medication	Use in migraine	Influence on sleep
Tricyclic antidepressants	Amitriptyline	Low doses 10–20 mg QHS can be recommended; [81]	Used off label as an insomnia treatment
	Doxepin	Use documented in clinical practice [85]; not tested as a migraine preventive	Studied in 4 insomnia RCTs insomnia with moderate benefit on sleep outcomes
Neutraceuticals	Melatonin	Use as a preventive not graded by the AAN/AHS Efficacy reported in one abortive trial in children and adolescents (similar to taking a nap) [86]; and as a preventive in one trial in adults	Treatment for circadian rhythm disorders. AASM guidelines suggest that clinicians not use melatonin for the treatment of insomnia Timing may have unintended effects on sleep phase
Beta-blockers		Propranolol and metoprolol are first line preventive agents as graded by AAN/AHS	Limited evidence that lipophilic beta-blockers (i.e., propranolol, metoprolol, atenolol and pinolol) carry insomnia as a side effect [84] Fatigue and bradycardia may compound perception of daytime fatigue
Others	Valproic acid, topiramate, venlafaxine	First and second line preventive agents	May have a sleep-inducing effects; recommend QHS use
	CGRP mAb and small molecule antagonists; onabotulinum toxinA	First line preventive agents (Onabotulinum toxinA for chronic migraine only)	Unknown/not expected to affect sleep

Vgontzas A, Pavlović J, Bertisch S. Sleep Symptoms and Disorders in Episodic Migraine: Assessment and Management. Curr Pain Headache Rep. 2023 Oct;27(10):511-520. doi: 10.1007/s11916-023-01160-z. Epub 2023 Sep 4. PMID: 37665530.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Amitriptyline

Potential Sleep Effects:

- Tricyclic antidepressants can suppress REM sleep
- Anti-histaminergic effect can cause daytime drowsiness

Drug class	Sleep continuity	SWS	REM latency	REM sleep	Mechanism of action related to effect on sleep
Sedative TCA (e.g., amitriptyline, doxepin, trimipramine)	↑	↑	↑	↓	antihistaminergic effect, inhibition of serotonin, and norepinephrine reuptake

Wichniak A, Wierzbicka A, Walęcka M, Jernajczyk W. Effects of Antidepressants on Sleep. Curr Psychiatry Rep. 2017 Aug 9;19(9):63. doi: 10.1007/s11920-017-0816-4. PMID: 28791566; PMCID: PMC5548844.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Beta Blockers

Potential Sleep Effects:

- Suppresses melatonin
- Insomnia
- Vivid dreams and nightmares

Practical Tip: Propranolol BID dosing, the first in the AM but the second dose, recommend taking this at 6PM and NOT immediately at bedtime

Chang CH, Yang YH, Lin SJ, Su JJ, Cheng CL, Lin LJ. Risk of insomnia attributable to β-blockers in elderly patients with newly diagnosed hypertension. Drug Metab Pharmacokinet. 2013;28(1):53-8. doi: 10.2133/dmpk.dmpk-12-rg-004. Epub 2012 Jul 17. PMID: 22813717.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Migraine Therapy and Sleep: Sleep as Acute Therapy

- Sedating medications or naps are intentionally used as an adjunctive analgesic strategy in acute settings
- A short, daytime nap may be a low-risk adjunct migraine treatment strategy though education to avoid the development of abnormal sleep patterns is important
- Some observational data shows these short naps loses its ability to terminate attacks once migraine becomes chronic

Vgontzas A, Pavlović J, Bertisch S. Sleep Symptoms and Disorders in Episodic Migraine: Assessment and Management. Curr Pain Headache Rep. 2023 Oct;27(10):511-520. doi: 10.1007/s11916-023-01160-z. Epub 2023 Sep 4. PMID: 37665530.

Migraine Therapy and Sleep: Non-Targeted Therapy

- In a 2025 meta-analysis of oral and non oral migraine preventative therapies and its effect on SUBJECTIVE sleep quality
- The meta-analysis showed a large effect size of 1.09 (95% confidence interval 0.57-1.62; overall $p < 0.001$; Cochran's $Q < 0.0001$) for migraine prophylaxis on improving sleep quality and on the PSQI and Insomnia severity index
- This effect was appeared to be independent of the type of preventive strategy, suggesting a common migraine–sleep pathway is involved

van Oosterhout WPJ, Kanis L, Wiendels NJ, Reijngoudt JW. Efficacy of oral and non-oral migraine prophylactic treatment on self-reported subjective sleep quality in migraine patients with sleep problems: A review and meta-analysis. J Sleep Res. 2025 Feb;34(1):e14241. doi: 10.1111/jsr.14241. Epub 2024 Jun 6. PMID: 38845376

Migraine Therapy and Sleep: Galcanezumab

- 2024 study of 54 patients (EM and CM) after 3 months of galcanezumab
- Notable benefit in sleep quality in all patients including domain specific sleep parameters in patients but particularly in those without depression or anxiety at baseline
- In those with comorbid depression or anxiety, while migraine improved, sleep may not have improved sufficiently

Ilgaz Aydinlar E, Erdogan Soyukibar T, Yalinay Dikmen P. Effectiveness of galcanezumab on sleep quality, migraine outcome, and multidimensional patient-reported outcome measures: a real-world experience in Turkish patients with episodic and chronic migraine. Front Neurol. 2024 Jun 3;15:1411238

Silvestro M, Tessitore A, Orologio I, De Micco R, Tartaglione L, Trojsi F, Tedeschi G, Russo A. Galcanezumab effect on "whole pain burden" and multidimensional outcomes in migraine patients with previous unsuccessful treatments: a real-world experience. J Headache Pain. 2022 Jun 13;23(1):69.

Migraine Therapy and Sleep: Erenumab

- 2022 study of 40 patients demonstrated a weak trend of improvement on the Epworth Sleepiness Scale and PSQI
- Home PSG showed objective improvement in sleep efficiency at 3 and 12 month follow up
- However, the authors posited that since it does not cross the BBB, it could not have a direct effect on sleep

Pellitteri G, Pez S, Nilo A, Surcinelli A, Gigli GL, Lettieri C, Valente M. Erenumab Impact on Sleep Assessed With Questionnaires and Home-Polysomnography in Patients With Migraine: The ERESON Study. Front Neurol. 2022 May 13;13:869677. doi: 10.3389/fneur.2022.869677.

Migraine Therapy and Sleep: Gepants

- 7766 reports of rimegepant, 3672 reports of atogepant, 1958 reports of ubrogepant, and 463 reports of zavegepant were identified after to examine reported adverse effects
- In neurological and psychiatric signals in this study, significance was found in patients describing “insomnia”, “somnolence”, and “anxiety” in rimegepant, atogepant, and ubrogepant
- The AEs associated with sleep alteration might be linked to the neuromodulatory effects of CGRP on glutamatergic signaling

Song Q, Gao S, Tan Y. Adverse events associated with gepants: a pharmacovigilance analysis based on the FDA adverse event reporting system. J Headache Pain. 2025 Jun 23;26(1):147. doi: 10.1186/s10194-025-02091-3. PMID: 40551098; PMCID: PMC12183883.

Chronobiology and Headache Therapy

- In a 2020 study on 61 patients undergoing onabotulinumtoxinA PREEMPT therapy, there were higher pain scores reported in patients injected in the morning vs the afternoon, both immediately after the treatment and 24 hours following
- Thus, the paper suggested to do these in the PM to reduce this side effect in susceptible individuals

Packard A, Smotherman C, Jovanovic N. Effect of circadian rhythm on the pain associated with preventive onabotulinumtoxinA injections for migraines. Chronobiol Int. 2020 Dec;37(12):1766-1771. doi: 10.1080/07420528.2020.1802290. Epub 2020 Sep 1. PMID: 32873093.

Chronobiology and Headache Therapy

- In endocrinologic studies examining essential hypertension, there are multiple observations of CGRP levels peaking around 23:10
- Timing of daily medications such as atogepant could be optimized to commensurately address this with direction to utilize a nightly dosing regimen

Trasforini G, Margutti A, Portaluppi F, Menegatti M, Ambrosio MR, Bagni B, Pansini R, Degli Uberti EC. Circadian profile of plasma calcitonin gene-related peptide in healthy man. J Clin Endocrinol Metab. 1991 Nov;73(5):945-51. doi: 10.1210/jcem-73-5-945. PMID: 1834691.

Case: AM

- You discontinue propranolol and switch to candesartan
- You provide a 14-day course of daridorexant which provided temporary relief
- CBTi and sleep stimulus control was maintained and continues to be effective
- Overall headache burden reduced and improvement in quality of life and migraine burden scores

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Sleep Apnoea Headache (ICHD-3)

Diagnostic criteria:

A. Headache present on awakening after sleep and fulfilling criterion C

B. Sleep apnoea with apnoea-hypopnoea index ≥5 has been diagnosed

C. Evidence of causation demonstrated by at least two of the following:

- headache has developed in temporal relation to the onset of sleep apnoea
- either or both of the following:
  - a) headache has worsened in parallel with worsening of sleep apnoea
  - b) headache has significantly improved or remitted in parallel with improvement in or resolution of sleep apnoea
- headache has at least one of the following three characteristics:
  - a) recurring on ≥15 days/month
  - b) all of the following:
    - – bilateral location
    - – pressing quality
    - – not accompanied by nausea, photophobia or phonophobia
  - c) resolving within 4 hours

D. Not better accounted for by another ICHD-3 diagnosis.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Sleep Apnoea Headache

- 10.1.4 Headache present upon awakening is a non-specific symptom in a variety of primary and secondary headache disorders, in sleep-related respiratory disorders other than sleep apnoea (*eg*, Pickwickian syndrome, chronic obstructive pulmonary disorder) and in other primary sleep disorders such as periodic leg movements of sleep.
- **It is unclear whether the mechanism of 10.1.4** Sleep apnoea headache **is related to hypoxia, hypercapnia or disturbance in sleep.**

10. Headache attributed to disorder of homoeostasis

10.1 Headache attributed to hypoxia and/or hypercapnia

10.1.1 High-altitude headache

10.1.2 Headache attributed to aeroplane travel

10.1.3 Diving headache

10.1.4 Sleep apnoea headache

CANADIAN HEADACHE CONFERENCE COAST TO COAST

Hypoxia Causing Headache?

› Cephalalgia. 2012 Apr;32(6):451-8. doi: 10.1177/0333102411431900. Epub 2011 Dec 15.

Sleep apnoea headache in the general population

Håvard Anton Kristiansen [1], Kari Jorunn Kværner, Harriet Akre, Britt Øverland, Leiv Sandvik, Michael Bjørn Russell

Affiliations + expand

PMID: 22174354 DOI: 10.1177/0333102411431900

- **Methods:** A postal questionnaire was received by 40,000 Norwegians from the general population. A total of 376 and 157 persons with high and low risk of sleep apnoea according to the Berlin Questionnaire had a polysomnography, and a clinical interview and examination by physicians.
- **Results:** Sleep apnoea headache was diagnosed in 11.8% of the participants with obstructive sleep apnoea (OSA), while morning headache with similar symptomatology was diagnosed in 4.6% of the participants without OSA ($p = 0.002$). After adjusting for potential confounders the odds ratio for OSA remained significantly increased among participants with morning headache with an adjusted odds ratio of 2.92 (1.31-6.51). When using a cut-off of moderate (apnoea hypopnea index, AHI $\geq$ 15) and severe (AHI $\geq$ 30) OSA, the prevalence of sleep apnoea headache was 11.6% and 13.3%, respectively. Average oxygen desaturation and lowest oxygen saturation was not significantly different in participants with OSA with and without morning headache.
- **Conclusion:** Morning headaches were significantly more frequent among participants with OSA than those without OSA. Sleep apnoea headache is less common in the general population than has previously been reported in clinic populations. The relation of hypoxia and morning headache is questioned.

Sleep Apnoea and Migraine

- Patients with OSA were found to have a 1.85-fold risk of incident migraine versus controls
- Headache improvement was reported by 49% due to either standard medical therapy or CPAP
- Mechanistic theories? Transmitted intrathoracic pressure, hypoxia, sleep disruption as a core principle

Chen TY, Hsieh TY, Wang YH, Chang R, Hung YM, Wei JC. Association between obstructive sleep apnea and migraine: A United States population-based cohort study. Headache. 2025 Apr;65(4):608-618. doi: 10.1111/head.14904. Epub 2025 Feb 10. PMID: 39925173.
Johnson KG, Ziemba AM, Garb JL. Improvement in headaches with continuous positive airway pressure for obstructive sleep apnea: a retrospective analysis. Headache. 2013 Feb;53(2):333-43. doi: 10.1111/j.1526-4610.2012.02251.x. Epub 2012 Sep 10. PMID: 22963547.

OSA Management

- Continuous Positive Airway Pressure
  - CPAP machine cost coverage varies by province
  - In Ontario, 75% covered if they complete an in-laboratory level one study (home studies are not eligible)
- Mandibular advancement device
  - Dental Consultation needed
- Surgical Management

Johnson KG, Ziemba AM, Garb JL. Improvement in headaches with continuous positive airway pressure for obstructive sleep apnea: a retrospective analysis. Headache. 2013 Feb;53(2):333-43. doi: 10.1111/j.1526-4610.2012.02251.x. Epub 2012 Sep 10. PMID: 22963547.

Restless Leg Syndrome (IRLSSG)

1. An irresistible urge to move the legs, usually but not always accompanied by uncomfortable and unpleasant sensations in the legs;
2. Symptoms that begin or worsen during periods of rest or inactivity, such as lying down or sitting;
3. Symptoms are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues;
4. Symptoms only occur or are worse in the evening or night than during the day; and
5. The occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping)

Gossard TR, Trotti LM, Videnovic A, St Louis EK. Restless Legs Syndrome: Contemporary Diagnosis and Treatment. Neurotherapeutics. 2021 Jan;18(1):140-155. doi: 10.1007/s13311-021-01019-4. Epub 2021 Apr 20. PMID: 33880737; PMCID: PMC8116476.

Restless Leg Syndrome and Migraine

- Dopamine has been implicated in the prodromal phase of and neuronal firing of the trigeminovascular complex
- Involved in wakefulness and pain via hypothalamic input and periaqueductal grey dopaminergic neurons
- Migraine patients are at increased risk of RLS, theoretically as a result of dysfunctional dopaminergic A11 neurons that transmit from the hypothalamus to the spinal cord
- Migraine patients with comorbid RLS have a higher incidence of prodrome than those without, because of shared dysfunction in dopamine or related pathways

Vgontzas A, Pavlović JM. Sleep Disorders and Migraine: Review of Literature and Potential Pathophysiology Mechanisms. Headache. 2018 Jul;58(7):1030-1039. doi: 10.1111/head.13358. Epub 2018 Aug 8. PMID: 30091160; PMCID: PMC6527324.

RLS and CGRP

Mov Disord. 2025 Jun;40(6):1148-1159. doi: 10.1002/mds.30125. Epub 2025 Jan 30.

Evidence of Involvement of the Calcitonin Gene-Related Peptide in Restless Legs Syndrome

Maria P Mogavero [1 2], Mojibola Fowowe [3], Akeem Sanni [3], Mona Goli [3], Giuseppe Lanza [4 5], Francesca L'Episcopo [4], Luigi Ferini-Strambi [1 2], Yehia Mechref [3], Raffaele Ferri [4]

Affiliations + expand

PMID: 39887452 PMCID: PMC12160970 DOI: 10.1002/mds.30125

Abstract

Background: Restless legs syndrome (RLS) is a common sensory-motor disorder characterized by an urge to move the legs, often with unpleasant sensations, particularly during rest. Current treatments include iron supplementation, dopamine agonists, and opioids, but new therapeutic approaches are needed. The dysfunction of the A11 nucleus, which modulates dopaminergic transmission to the spinal cord, is thought to play a role in RLS pathophysiology. Calcitonin gene-related peptide (CGRP), which is involved in pain modulation, may interact with A11 pathways, suggesting a role in RLS.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

RLS and CGRP Monoclonal Antibodies

J Headache Pain. 2025 Feb 19;26(1):36. doi: 10.1186/s10194-025-01976-7.

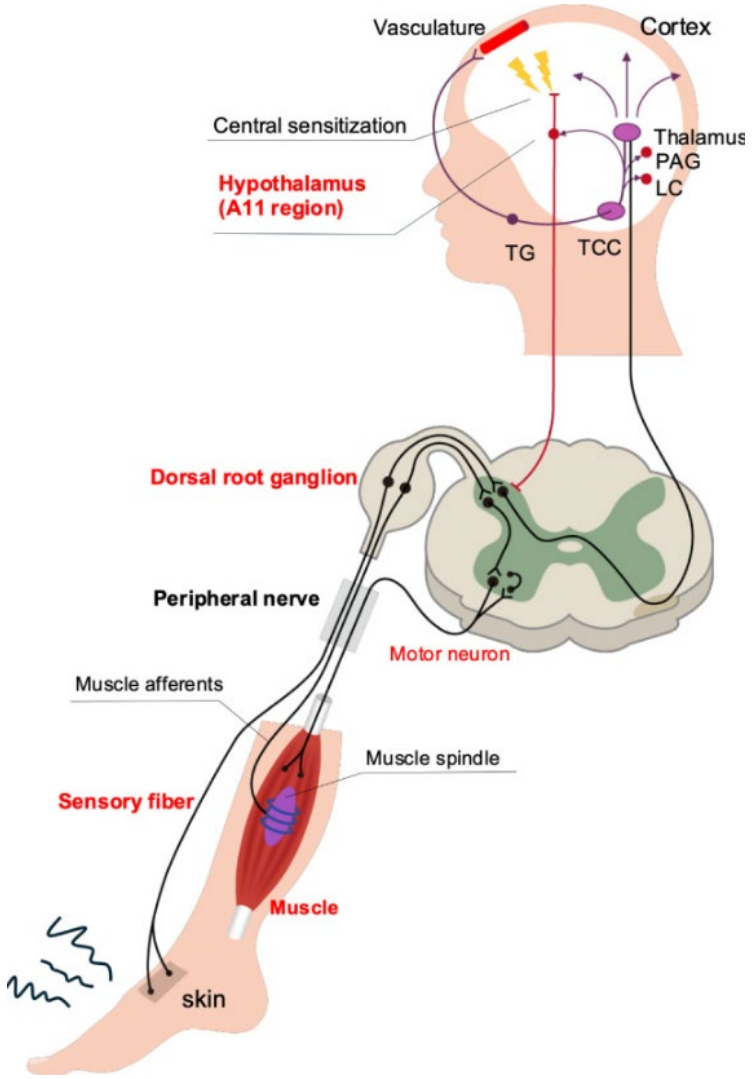
The effect of calcitonin gene-related peptide monoclonal antibodies on restless legs syndrome in patients with migraine

Keisuke Suzuki [1], Shiho Suzuki [2], Hiroaki Fujita [2], Saro Kobayashi [2], Mukuto Shioda [2], Ryotaro Hida [2], Koichi Hirata [2]

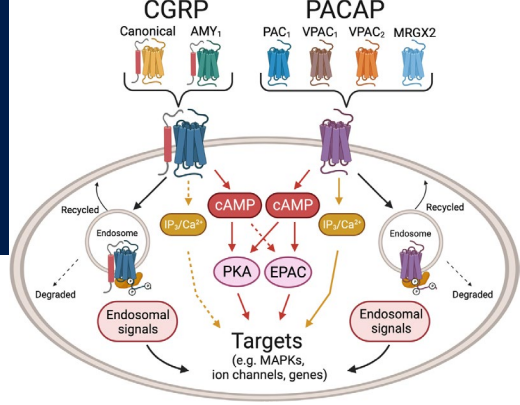
Affiliations + expand

PMID: 39972460 PMCID: PMC11837639 DOI: 10.1186/s10194-025-01976-7

Conclusion: Our study revealed that 3-month CGRP mAb treatment significantly alleviated RLS symptoms, central sensitization and headache-related disability in patients with comorbid migraine and RLS



Sleep and Migraine: PACAP

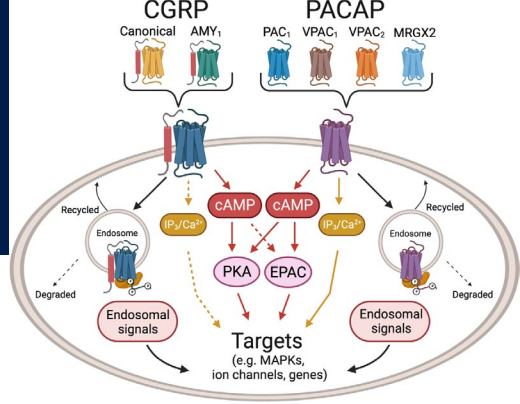


- Pituitary adenylate cyclase-activating peptide
- Parasympathetic and hypothalamic signaling molecule, implicated in both migraine and cluster headache
- In migraine, infusions of PACAP (both 27 and 38 isoforms) can trigger an attack in susceptible individuals
- Cluster headache has a particularly strong association with temporal patterns and chronobiology

Holland PR, Barloese M, Fahrenkrug J. PACAP in hypothalamic regulation of sleep and circadian rhythm: importance for headache. J Headache Pain. 2018 Mar 5;19(1):20. doi: 10.1186/s10194-018-0844-4. PMID: 29508090; PMCID: PMC5838029.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Sleep and Migraine: PACAP



- PACAP has a key role in hypothalamic circadian entrainment to light
- In rodents, PACAP immunoreactivity was identified in a subset of RHT retinal ganglion cells that were responsive to light and projected to the SCN
- These PACAP containing neurons were shown to express melanopsin (as opposed to glutamate which is the typical neurotransmitter of the RHT)
- Local application in-vitro was shown to phase advance SCN neurons during the subjective day via a PAC_1 dependent mechanism, but not at night, suggesting a role for PACAP in daytime regulation of the circadian cycle

Holland PR, Barloese M, Fahrenkrug J. PACAP in hypothalamic regulation of sleep and circadian rhythm: importance for headache. J Headache Pain. 2018 Mar 5;19(1):20. doi: 10.1186/s10194-018-0844-4. PMID: 29508090; PMCID: PMC5838029.

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Summary and Clinical Take-Home Points

- Sleep and migraine are likely inextricably related on multiple physiologic levels
- Insomnia and migraine are likely bidirectional and treating one likely impacts the other
- Sleep apnea headache is a distinct ICHD3 diagnoses but treating OSA can be simple and likely will improve headache outcomes as well
- RLS may be correlated via a shared central pathway but its mechanism is not clearly known

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

With Many Thanks to:

- Dr Mark Boulos
- Dr Jonathan Yeung Laiwah

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

Questions?

james.im@mail.utoronto.ca

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

CANADIAN HEADACHE CONFERENCE
COAST TO COAST

THANK YOU