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The Impact of Sleep-Wake State Instability in Narcolepsy

February 16, 2019

An educational event sponsored by Harmony Biosciences, LLC.

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Thomas Jefferson University

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Ohio Sleep Medicine Institute

Learn more at KnowNarcolepsy.com

18-NAR-1800112/Jan 2019

Program Overview

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- Review the pathophysiology of narcolepsy and sleep-wake state instability
- Highlight the role of REM sleep dysregulation
- Share insights about symptom manifestations and their impact
- Discuss the important role of histamine in sleep-wake state stability

Disclosures

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- Harmony Biosciences is the sponsor of this program, and the content of this program was developed by Harmony Biosciences in collaboration with the presenter(s)
- This is not a continuing medical education (CME) event; therefore, no CME credit will be provided
- Today's faculty are paid consultants for Harmony Biosciences

Question for the Audience

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Who will win the NBA Championship this year?

1. Golden State Warriors
2. Philadelphia 76ers
3. Houston Rockets
4. Milwaukee Bucks
5. Toronto Raptors
6. Cleveland Cavilers

Question for the Audience

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How important is REM sleep dysregulation to the manifestation of narcolepsy symptoms?

1. Not at all important
2. A little important
3. Somewhat important
4. Very important

Question for the Audience

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How important is it to assess impairments in psychosocial functioning in narcolepsy?

1. Not at all important
2. A little important
3. Somewhat important
4. Very important

Question for the Audience

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How important is the role of histamine in promoting and stabilizing wakefulness during the day?

1. Not at all important
2. A little important
3. Somewhat important
4. Very important

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There's More to Know!

Pathophysiology of Narcolepsy and Impact on Sleep-Wake State Stability

Asim Roy, MD

Normal Sleep-Wake States:
Stable Boundaries and Predictable Transitions

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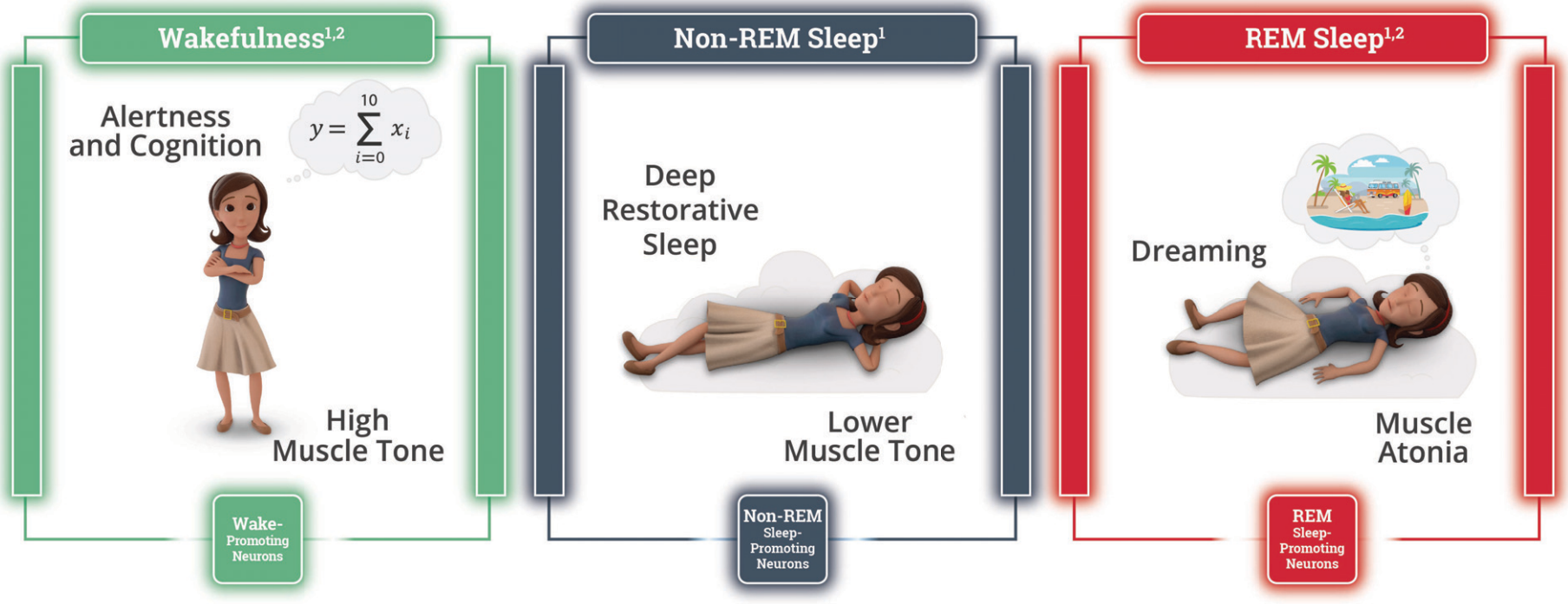


Normally promoted during biologic day[2,3]

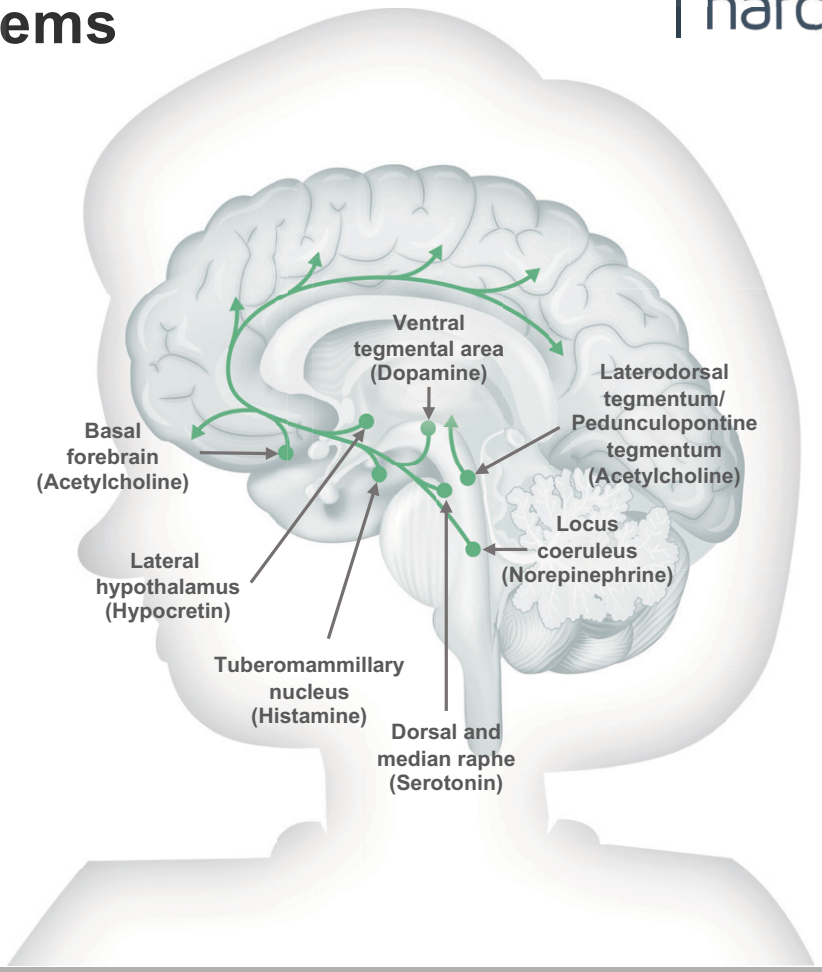
Normally occurs during biologic night[2,3]

Normally occurs during biologic night[2,3]

1. Brown RE et al. *Physiol Rev.* 2012;92(3):1087-1187. **2.** Scammell T et al. *Neuron Rev.* 2017;93(4):747-765. **3.** Morris CJ et al. *Prog Brain Res.* 2012;199:337-358.

Wakefulness Is Promoted by Multiple Wake-Promoting Neuronal Systems

- Wakefulness is promoted by the coordination of interconnected neuronal systems,[1-3] including:
  - Acetylcholine
  - Dopamine
  - Histamine
  - Norepinephrine
  - Serotonin



Adapted with permission from Saper CB et al. *Nature*. 2005;437(7063):1257-1263.

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Neuronal Systems in the Hypothalamus Help Stabilize Wakefulness

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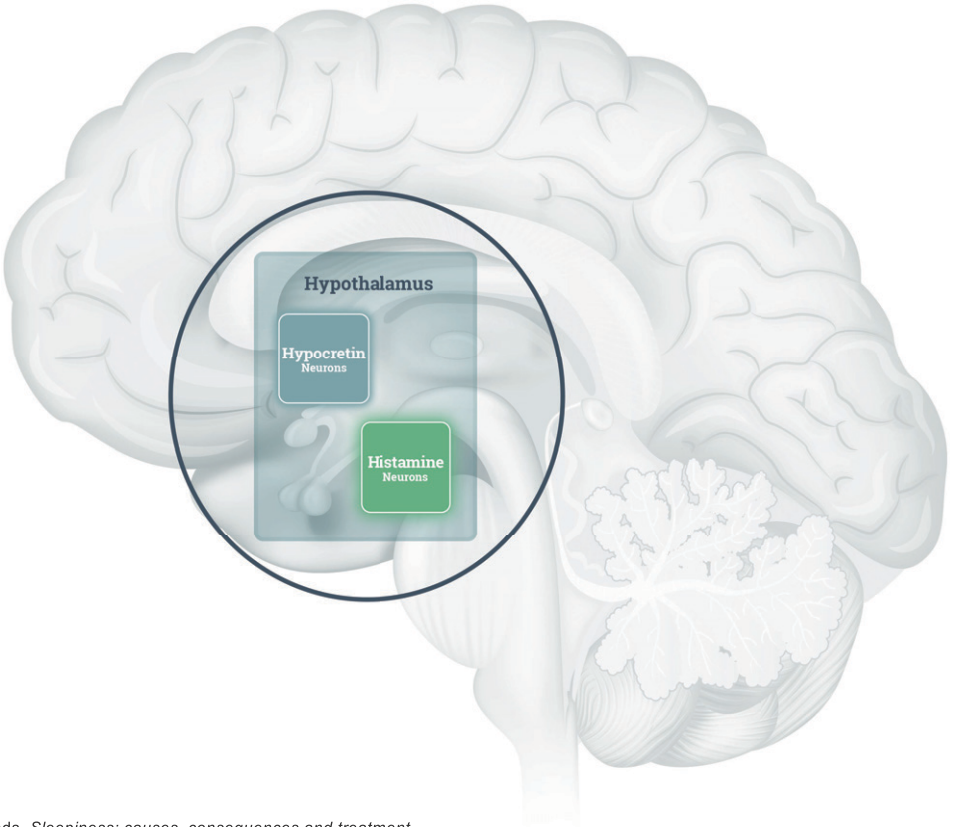
- The hypothalamus is a critical "control center" for sleep-wake state stability[1-4]
  - Contains neuronal systems that help maintain stable wakefulness, including neurons that produce hypocretin and histamine[3,5-7]
- Hypocretin and histamine neurons in the brain originate *only* in the hypothalamus[1,6,8]



1. Shan L et al. *Nat Rev Neurol.* 2015;11(7):401-413. **2.** van der Heide A, Lammers GJ. Narcolepsy. In: Thorpy MJ, Billiard M, eds. *Sleepiness: causes, consequences and treatment*. Cambridge University Press;2011:111-125. **3.** Scammell TE et al. *Neuron Rev*. 2017;93(4):747-765. **4.** Saper CB et al. *Nature*. 2005;437(7063):1257-1263. **5.** España RA et al. *Sleep*. 2011;34(7):845-858. **6.** Haas HL et al. *Physiol Rev*. 2008;88(3):1183-1241. **7.** Schwartz MD, Kilduff TS. *Psychiatr Clin North Am*. 2015;38(4):615-644. **8.** Scammell TE. *Ann Neurol.* 2003;53(2):154-166.

Hypocretin Neurons Promote Stable Wakefulness

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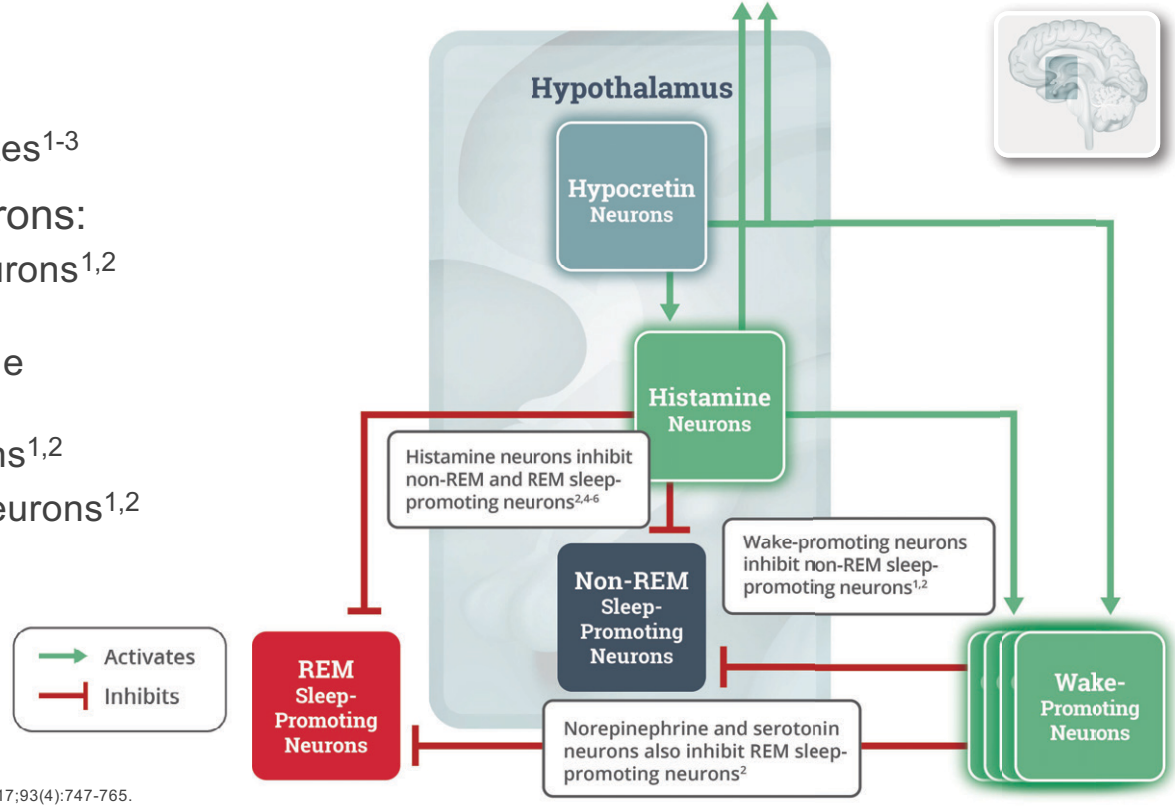
- Hypocretin neurons help ensure:
  - Stable boundaries and predictable transitions between sleep-wake states[1-3]
- During wakefulness, hypocretin neurons:
  - Activate cortical and subcortical neurons[1,2]
  - Activate hypothalamic histamine and wake-promoting neurons outside of the hypothalamus[1,2]
  - Inhibit REM sleep-promoting neurons[1,2]
  - Inhibit non-REM sleep-promoting neurons[1,2]



Based on animal and human studies.

1. España RA, Scammell TE. *Sleep*. 2011;34(7):845-858. **2.** Scammell T et al. *Neuron Rev*. 2017;93(4):747-765.
3. van der Heide A, Lammers GJ. In: Thorpy MJ, Billiard M, eds. Cambridge University Press;2011:111-125.
4. Haas HL et al. *Physiol Rev*. 2008;88(3):1183-1241. **5.** Crochet S et al. *Eur J Neurosci*. 2006;24(5):1404-1412.
6. Williams RH et al. *J Neurosci*. 2014;34(17):6023-6029.

Loss of Hypocretin Neurons Leads to Sleep-Wake State Instability

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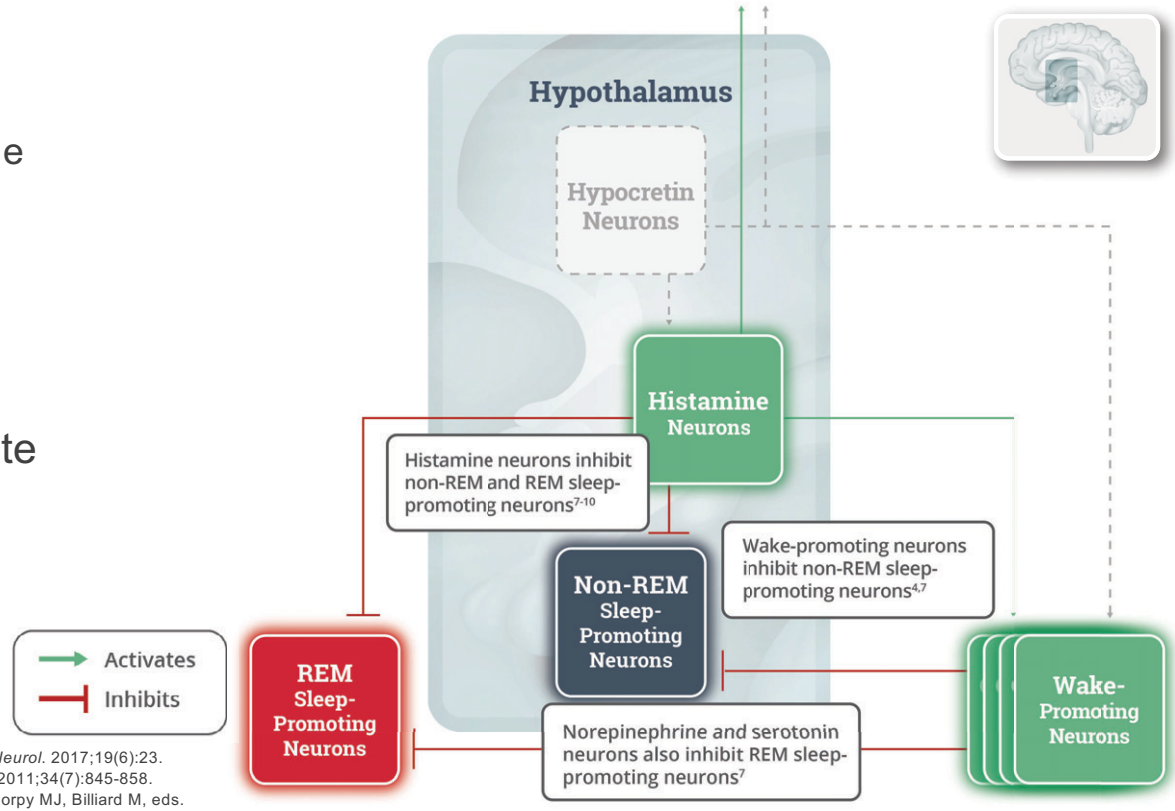
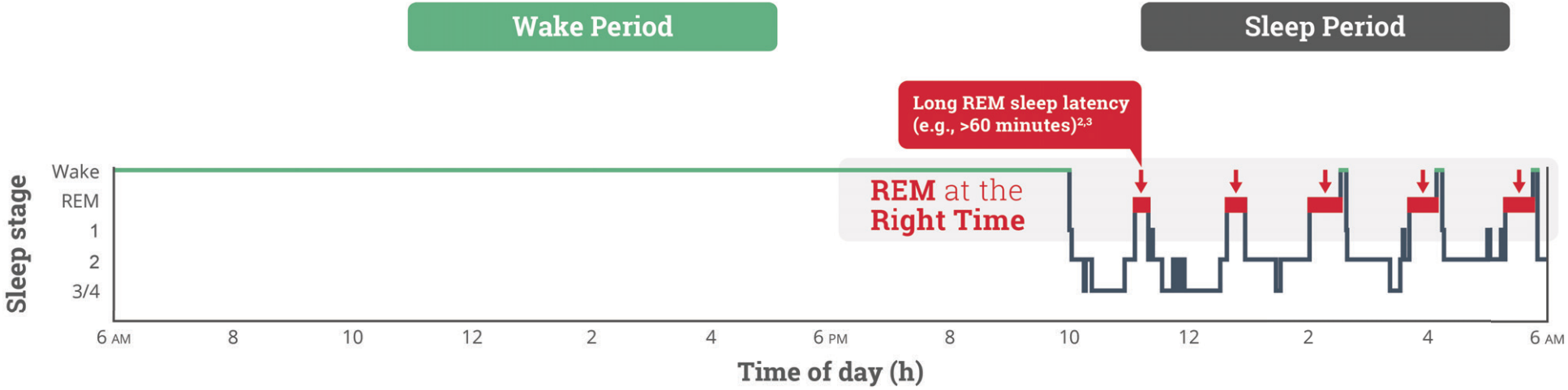
- Lack of hypocretin leads to:
  - Insufficient activation of histamine and wake-promoting neurons outside of the hypothalamus[1]
  - Insufficient inhibition of REM sleep-promoting neurons[2,3]
  - Insufficient inhibition of non-REM sleep-promoting neurons[4,5]
- This process causes sleep-wake state instability[4,5]
  - Frequent transitions[4,6]
  - Unstable boundaries[6]



Based on animal and human studies.

1. Scammell TE. *N Engl J Med*. 2015;373(27):2654-2662. **2.** Pillen S et al. *Curr Treat Options Neurol*. 2017;19(6):23. **3.** Burgess CR et al. *J Neurosci*. 2013;33(23):9734-9742. **4.** España RA, Scammell TE. *Sleep*. 2011;34(7):845-858. **5.** Saper CB et al. *Nature*. 2005;437(7063):1257-1263. **6.** van der Heide A, Lammers GJ. In: Thorpy MJ, Billiard M, eds. Cambridge University Press;2011:111-125. **7.** Scammell TE et al. *Neuron*. 2017;93(4):747-765. **8.** Haas HL et al. *Physiol Rev*. 2008;88(3):1183-1241. **9**. Crochet S et al. *Eur J Neurosci*. 2006;24(5):1404-1412. **10**. Williams RH et al. *J Neurosci*. 2014;34(17):6023-6029.

Normal Sleep-Wake Cycle
Infrequent Transitions Between Sleep-Wake States



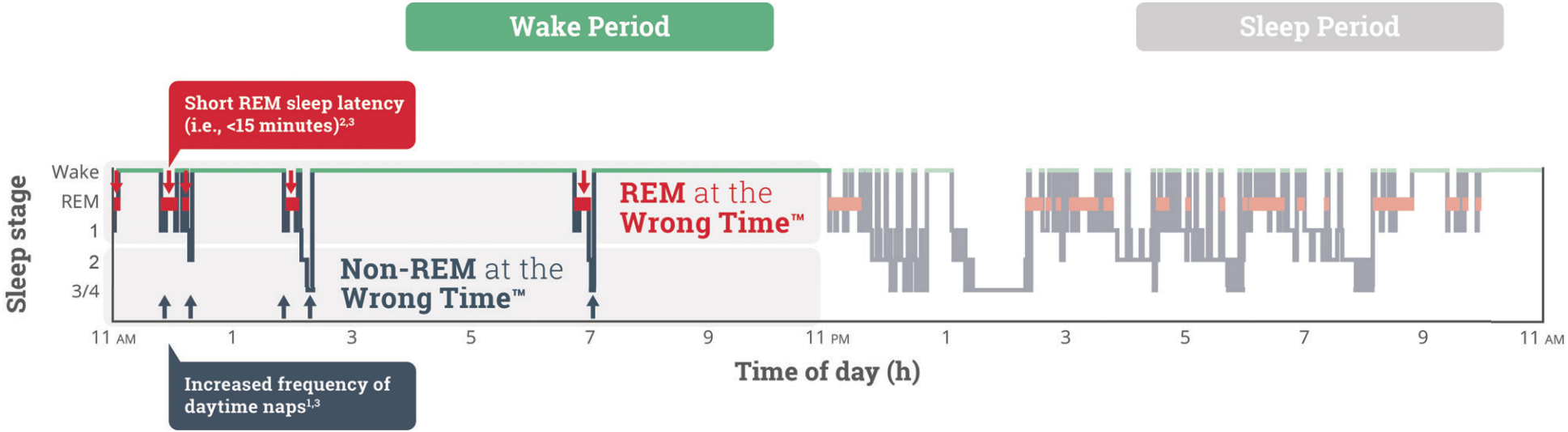
- Consolidated wakefulness during the day with generally no daytime naps or intrusions of non-REM sleep and REM sleep[1,4]
- Typically associated with alertness and cognition[4,5]

- Generally infrequent awakenings[2]
- Alternating and predictable periods of non-REM and REM sleep[2,4]
- REM sleep periods get longer over the course of the night[2,4]

Adapted with permission from Plazzi G et al. *Sleep Med Rev*. 2008;12(2):109-128.

1. Rogers AE et al. *Sleep*. 1994;17(7):590-597. **2.** Plazzi G et al. *Sleep Med Rev*. 2008;12(2):109-128. **3.** Pizza F et al. *Sleep*. 2015;38(8):1277-1284.
4. Scammell TE et al. *Neuron*. 2017;93(4):747-765. **5.** Brown RE et al. *Physiol Rev*. 2012;92(3):1087-1187.

Narcolepsy Sleep-Wake Cycle
Sleep-Wake State Instability



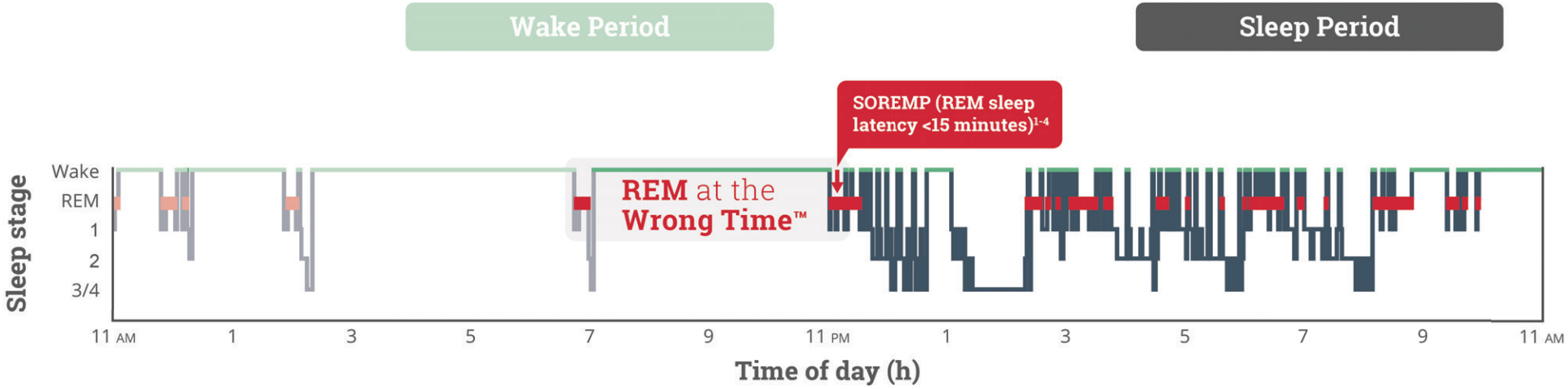
Unstable wakefulness during the day

- Increased frequency of daytime naps[1,3]
  - ***Non-REM at the Wrong Time™***
- Short REM sleep latency[2,3]
  - ***REM at the Wrong Time™***

Adapted with permission from Rogers AE et al. *Sleep*. 1994;17(7):590-597.

1. Rogers AE et al. *Sleep*. 1994;17(7):590-597. **2.** Green PM, Stillman MJ. *Arch Fam Med*. 1998;7(5):472-478. **3.** Pizza F et al. *Sleep*. 2015;38(8):1277-1284.

Narcolepsy Sleep-Wake Cycle
Sleep-Wake State Instability



Disrupted nighttime sleep[4]

- Nocturnal SOREMP (low diagnostic sensitivity)[2,5]
- Frequent awakenings[2,4]
- Frequent transitions between states (wakefulness, non-REM sleep, and REM sleep)[3,4]

SOREMP, sleep-onset REM period.

Adapted with permission from Rogers AE et al. *Sleep*. 1994;17(7):590-597.

1. Rogers AE et al. *Sleep*. 1994;17(7):590-597. **2.** Plazzi G et al. *Sleep Med Rev*. 2008;12(2):109-128. **3.** Pizza F et al. *Sleep*. 2015;38(8):1277-1284. **4.** Roth T et al. *Sleep Med*. 2013;9(9):955-965.
5. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. 2014

Unstable Boundaries and Sleep-Wake State Instability

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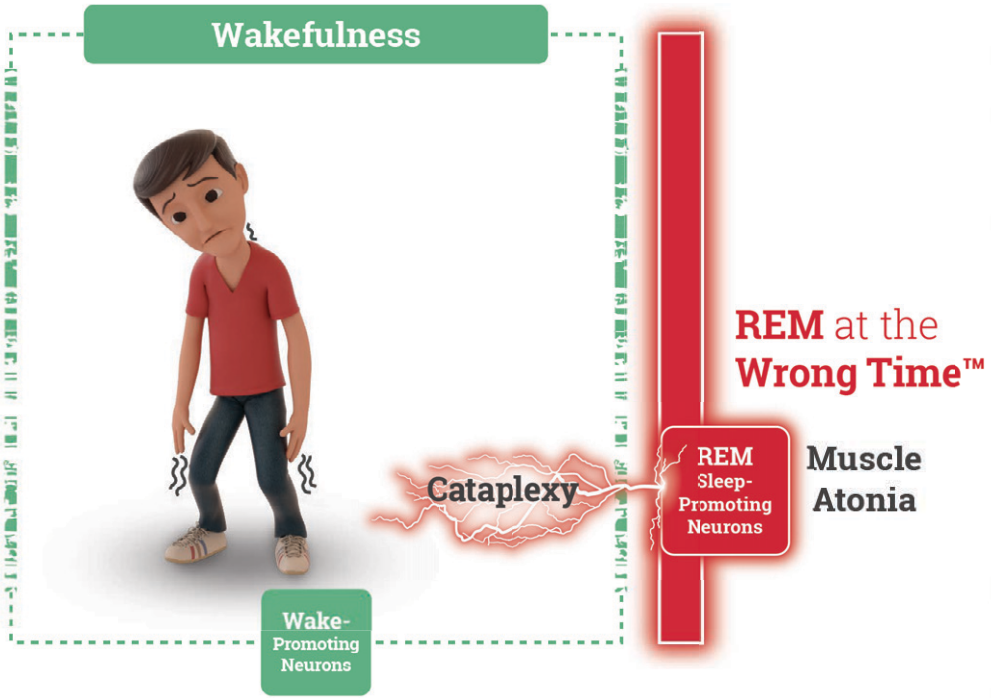
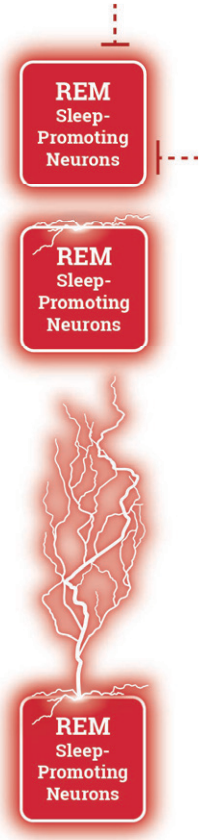
Elements of REM Sleep Intruding Into Wakefulness Manifest as Symptoms of REM Sleep Dysregulation (e.g., Cataplexy)[1,2]





- Insufficient inhibition of REM sleep-promoting neurons[2-4]
- Leads to intermittent activation of REM sleep-promoting neurons[2-4]
- Causes elements of REM sleep to intrude into wakefulness[2-4]

1. España RA, Scammell TE. *Sleep*. 2011;34(7):845-858. **2.** Scammell TE. *N Engl J Med*. 2015;373(27):2654-2662.
3. Burgess CR et al. *J Neurosci*. 2013;33(23):9734-9742. **4.** Pillen S et al. *Curr Treat Options Neurol*. 2017;19(6):23.

Elements of Sleep May Intrude Into Wakefulness

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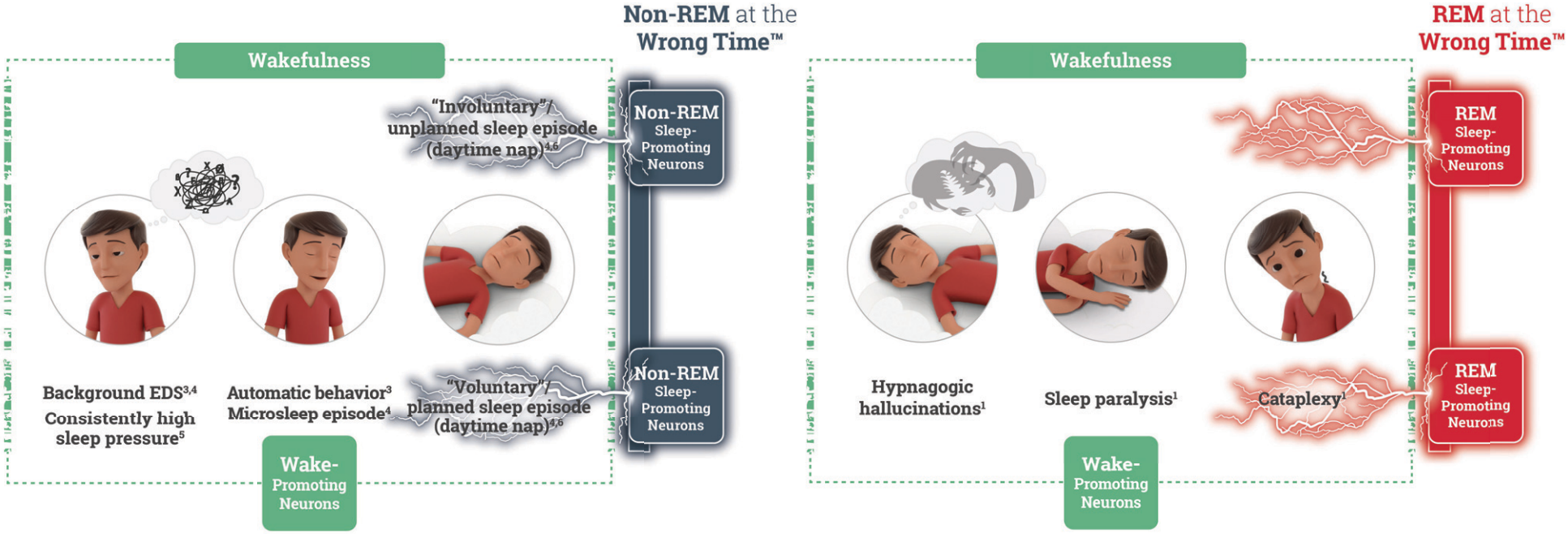
- Sleep-wake state instability in narcolepsy leads to elements of one state intruding into another[1,2]



EDS, excessive daytime sleepiness.

1. Scammell TE. *N Engl J Med.* 2015;373(27):2654-2662. **2.** Broughton R et al. *Sleep.* 1986;9(1 Pt 2):205-215. **3.** Thorpy M et al. *Sleep Med Clin.* 2017;12(1):61-71. **4.** Nishino S. *Sleep Med.* 2007;8(4):373-399. **5.** Kretzschmar U et al. *J Sleep Res.* 2016;25(3):307-313. **6.** Thorpy M, Dauvilliers Y. *Sleep Med.* 2015;16(1):9-18.

Question for the Audience

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How important is REM sleep dysregulation to the manifestation of narcolepsy symptoms?

1. Not at all important
2. A little important
3. Somewhat important
4. Very important

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There's More to Know!

Manifestations of Narcolepsy Symptoms

Asim Roy, MD

Narcolepsy May Go Unrecognized For Years

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- People living with narcolepsy may experience symptoms for years before receiving a diagnosis[1,2]
  - Delay of approximately 8 to 15 years between symptom onset and diagnosis[1,3]
- Comorbidities may delay diagnosis due to overlapping symptoms[1,4]
  - Obstructive sleep apnea and other sleep disorders may also contribute to EDS symptoms[1,5]

Common Comorbidities Among People Living With Narcolepsy

Depression[3,6]

Anxiety disorders[3,6]

Obstructive sleep apnea[2,3]

ADHD symptoms[7]

1. Thorpy M, Morse AM. *Sleep Med Clin*. 2017;12(1):61-71. **2.** Maski K et al. *J Clin Sleep Med*. 2017;13(3):419-425. **3.** Carter LP et al. *Postgrad Med*. 2014;126(3):216-224. **4.** Overeem S et al. *Sleep Med Clin*. 2012;7(2012):263-281. **5.** Plazzi G et al. *Sleep Med Rev*. 2008;12(2):109-128. **6.** Ohayon MM. *Sleep Med*. 2013;14(6):488-492. **7.** Filardi M et al. *PLoS ONE*. 2017;12(8):e0182085.

EDS Can Manifest in Many Different Ways

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Obvious Manifestations ..... **Less Obvious Manifestations**

Lapses Into Drowsiness or Sleep[1-3]

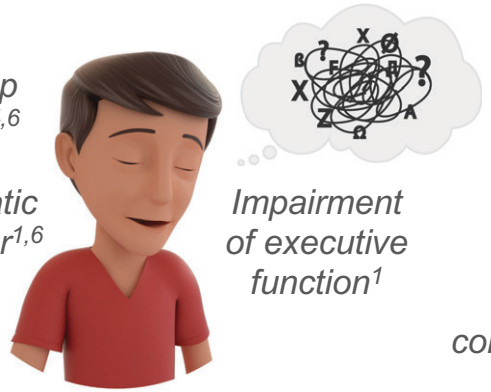
Involuntary (unplanned) naps[4,5]

Voluntary (planned) naps[4,5]

Inability to Stay Awake and Alert During the Day[2]

Microsleep episodes[4,6]

Automatic behavior[1,6]

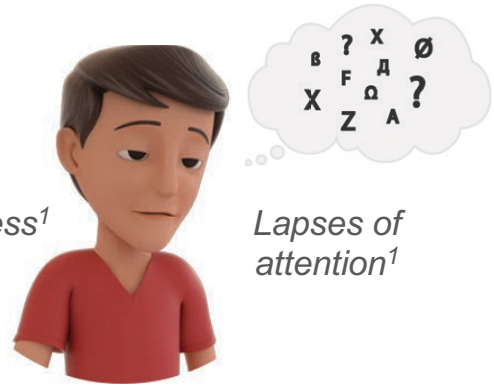


Impairment of executive function[1]

Impaired Alertness and Neurocognitive Functioning[1,2,6]

Forgetfulness[1]

Difficulty concentrating[6]



Lapses of attention[1]

1. Thorpy M et al. *Sleep Med Clin.* 2017;12(1):61-71. **2.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders.* 3rd ed. 2014. **3.** Kretzschmar U et al. *J Sleep Res.* 2016;25(3):307-313.
4. Nishino S. *Sleep Med.* 2007;8(4):373-399. **5.** Thorpy M, Dauvilliers Y. *Sleep Med.* 2015;16(1):9-18. **6.** Ahmed I, Thorpy M. *Clin Chest Med.* 2010;31(2):371-381.

REM Sleep Dysregulation Can Have a Significant Impact

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Hypnagogic Hallucinations

- Vivid dream-like experiences while falling asleep[1]*
- May appear as visual or auditory hallucinations[2,3]
  - Dark shadows
  - Figures, animals, or people
  - Threatening statements
- Can be extremely realistic and frightening[2,3]

*Hypnopompic hallucinations occur upon awakening.[1,3]

Sleep Paralysis

- Temporary inability to move or speak at sleep-wake transitions[1,2]
  - Usually occurs at the point of waking but may occur at sleep onset[4]
  - Most episodes last only a few minutes[2]
- Patients are conscious and aware of their environment[1,2]
- Patients may be frightened or have anxiety associated with a fear of dying[5]

These symptoms often occur together, which may make these events even more terrifying.[3-5]

1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. 2014. **2.** Dauvilliers Y, Lopez R. In: Baumann CR et al, eds. *Narcolepsy: Pathophysiology, Diagnosis, and Treatment*. Springer Science+Business Media, LLC; 2011:291-299. **3.** Ahmed I, Thorpy M. *Clin Chest Med*. 2010;31(2):371-381. **4.** Overeem S et al. *Sleep Med Clin*. 2012;7(2012):263-281. **5**. Pelayo R et al. In: Lee-Chiong TL, ed. *Sleep: A Comprehensive Handbook*. John Wiley & Sons, Inc; 2006:145-149.

Cataplexy Can Manifest in Many Different Ways

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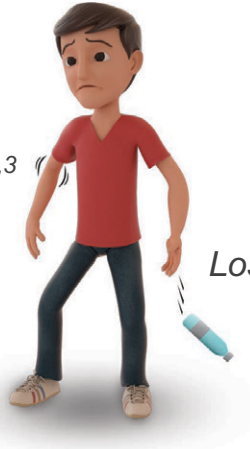
Obvious Manifestations ..... **Less Obvious Manifestations**

Affecting Many/ Most Muscle Groups[1,2]

Most people with cataplexy do not experience rapid collapse to the ground.[1,2]

Head/Neck Commonly Affected[3,4]

Affecting Limited Muscles[1,4]



Not all people living with narcolepsy experience cataplexy.[3]

1. Thorpy M et al. *Sleep Med Clin*. 2017;12(1):61-71. **2.** Overeem S et al. *Sleep Med*. 2011;12(1):12-18. **3.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. 2014.
4. Ahmed I et al. *Clin Chest Med*. 2010;31(2):371-381

Cataplexy Can Manifest in Many Different Ways

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Obvious Manifestations ..... **Less Obvious Manifestations**

Affecting Many/ Most Muscle Groups[1,2]

Complete attack resulting in collapse or fall to the ground[1,3,4]

Most people with cataplexy do not experience rapid collapse to the ground[1,2]

Head/Neck Commonly Affected[3,4]

Head drops[3]

Sagging of face or jaw[2]

Slurred speech[3]

Affecting Limited Muscles[1,4]

Twitching[1,3]

Loss of grip[1]

Not all people living with narcolepsy experience cataplexy.[3]

1. Thorpy M et al. *Sleep Med Clin*. 2017;12(1):61-71. **2.** Overeem S et al. *Sleep Med*. 2011;12(1):12-18. **3.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. 2014.
4. Ahmed I et al. *Clin Chest Med*. 2010;31(2):371-381

Question for the Audience

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What proportion of your patients with narcolepsy with cataplexy experience postural muscle paralysis that results in collapse to the ground?

1. 76-100%
2. 51-75%
3. 26-50%
4. 0-25%

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There's More to Know!

Recognizing Cataplexy and Its Impact

Karl Doghramji, MD

The Know Narcolepsy Survey

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Patient Survey

Conducted in March/April 2018

200 US adults with self-reported narcolepsy

- 26% n=52 Narcolepsy type 1
- 44% n=89 Narcolepsy type 2
- 30% n=59 Unsure of subtype

HCP Survey

Conducted in August 2018

251 physicians currently in clinical practice who have treated patients with narcolepsy within the last two years

- Medical specialties included family medicine, internal medicine, neurology, psychiatry, pulmonology, and others

45% n=113 Board-certified sleep specialists

General Public Survey

Conducted in March/April 2018

1203 US adults

- Stratified and weighted to ensure accurate representation of the full US population (based on the most recent US Census data) in terms of gender, age, region, income, education, race, and ethnicity

- Surveys were conducted online by Versta Research on behalf of Harmony Biosciences
- Respondents were recruited from a national research panel

Data on file. Harmony Biosciences. 2018.

Know Narcolepsy Patient Survey

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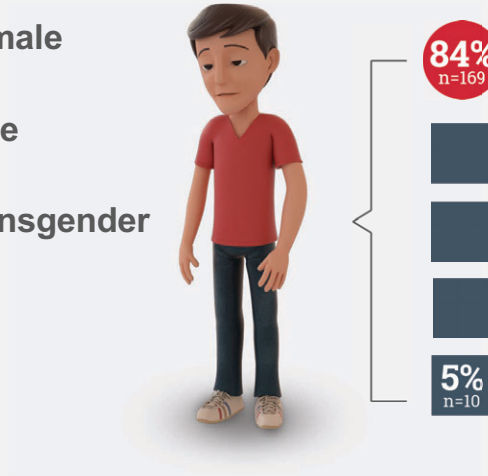
People Living With Narcolepsy

Patient survey conducted March 19 – April 6, 2018

Survey Respondents: 200 adults in the US with narcolepsy, mean age 47 (18-84 years)

- 69% n=138 Female
- 30% n=60 Male
- 1% n=2 Transgender



- 84% n=169 Were taking medications for their narcolepsy
  - 41% n=82 Stimulants
  - 40% n=81 Wake-promoting agents
  - 35% n=70 Antidepressants
  - 5% n=10 Sodium oxybate

Data on file. Harmony Biosciences. 2018.

Narcolepsy Diagnostic Delay

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People Living With Narcolepsy

Know Narcolepsy Patient Survey

Subtype[1]

- 26% (n=52) Type 1
- 44% (n=89) Type 2
- 30% (n=59) Unknown

Literature suggests about two-thirds of people living with narcolepsy have narcolepsy type 1 (narcolepsy with cataplexy)[2]

38% (n=77) **Reported being misdiagnosed with something else first[1]**

On average, it took more than 6 years from symptom onset to be correctly diagnosed with narcolepsy[1]

1. Data on file. Harmony Biosciences. 2018. **2.** Silber MH et al. *Sleep*. 2002;25(2):197-202.

Some Manifestations of Cataplexy May Be Under Recognized

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People Living With Narcolepsy

Know Narcolepsy Survey

According to patient survey respondents:

26% n=51 — **Reported "cataplexy" as a symptom[1]**

However, of those who did not report cataplexy…

78% n=116 — **Reported that they tend to drop things and are more clumsy than others[1]**

44% n=65 — **Experience brief muscle weakness (such as relaxation of the face, eyelids, neck, or knees, or slurred speech) triggered by emotions[1]**

According to HCP survey respondents (n=251):

39% n=98 — **Reported specifically talking about cataplexy at all or most appointments with narcolepsy patients who have not previously presented with cataplexy[1]**

In a questionnaire study of 109 patients with cataplexy, 70% of patients reported involvement of the jaw or face in cataplexy episodes[2]

1. Data on file. Harmony Biosciences. 2018. **2.** Overeem S et al. *Sleep Med*. 2011;12(1):12-18.

Question for the Audience

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How often do you specifically talk about cataplexy with narcolepsy patients who have not previously presented with cataplexy?

1. 76-100% of appointments
2. 51-75% of appointments
3. 26-50% of appointments
4. 0-25% of appointments
5. Only at the initial consultation

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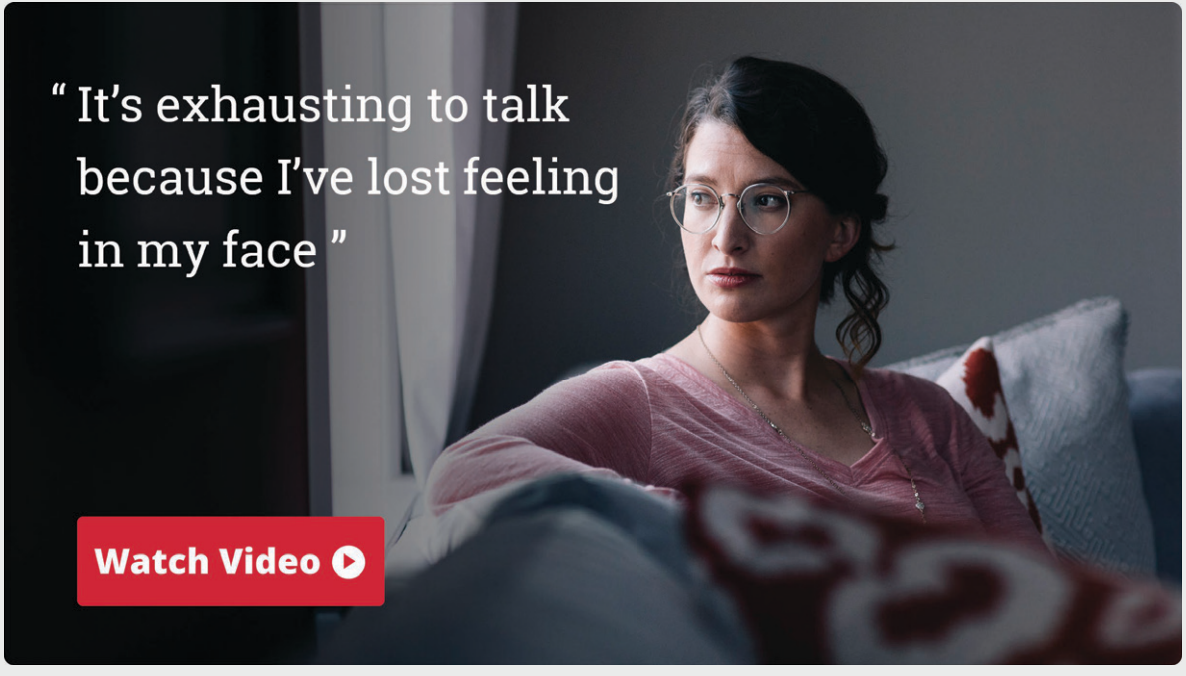
There's More to Know!



Nicki

29 years old,
living with narcolepsy
with cataplexy

Cataplexy Can Be Triggered by a Range of Emotions and Situations

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Multiple questionnaire studies in patients with narcolepsy identify the range of emotional and situational triggers of cataplexy[1,2]

Emotions

- Happiness[3]
- Laughter/humor[1,4]
- Anger[1]
- Excitement[2]
- Stress or anxiety[1]
- Tension[2]
- Anticipation[1]
- Embarrassment[2]

Situations

- Telling or hearing a joke, making a witty remark[1]
- Being tickled[1]
- Being the center of attention[1]
- Unexpectedly encountering a friend or acquaintance[1]
- Being startled[1]
- Remembering happy or emotional events[2]
- Intimate moments[2]

1. Overeem S et al. *Sleep Med*. 2011;12(1):12-18. **2.** Anic-Labat S et al. *Sleep*. 1999;22(1):77-87.
3. Thorpy M et al. *Sleep Med Clin*. 2017;12(1):61-71. **4.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. 2014.

Recognizing Cataplexy in Patients*

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Ask your patients with narcolepsy…

- Have you ever experienced muscle weakness in response to certain emotions, such as[1]…
  - ☐ Laughter/humor?[2,3]
  - ☐ Excitement?[4]
  - ☐ Anger?[3]
  - ☐ Stress or anxiety?[3]
- Have you ever experienced muscle weakness in response to certain situations, such as[1]…
  - ☐ Telling or hearing a joke?[3]
  - ☐ Anticipation?[3]
  - ☐ Being startled?[3]
  - ☐ Intimate moments?[4]
- If someone tells you a funny joke or you get very angry, do you ever experience[1,3]…
  - ☐ Neck weakness causing your head to drop?[2]
  - ☐ Slurred speech?[3]
  - ☐ Sagging of your jaw[3]
  - ☐ Droopy or heavy eyelids?[5]
  - ☐ Hand weakness or loss of grip?[3,5]

*Common triggers and patterns of muscle weakness reported in questionnaire studies in patients with narcolepsy with cataplexy.[3,4]

1. Thorpy M, Dauvilliers Y. *Sleep Med*. 2015;16(1):9-18. **2.** American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. 2014.
3. Overeem S et al. *Sleep Med*. 2011;12(1):12-18. **4.** Anic-Labat S et al. *Sleep*. 1999;22(1):77-87. **5.** Thorpy M, Morse AM. *Sleep Med Clin*. 2017;12(1):61-71.

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There's More to Know!

Psychosocial Consequences

Karl Doghramji, MD

Question for the Audience

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What do you think is the biggest challenge that people with narcolepsy face in their daily lives?

1. Patients are unable to complete normal daily tasks.
2. Patients struggle to get through school.
3. Patients struggle to keep jobs.
4. Patients worry about their safety or the safety of others with them.

Question for the Audience

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What challenge do you think patients care most about?

1. Being unable to complete normal daily tasks
2. Struggling to get through school
3. Struggling to keep jobs
4. Worrying about their safety or the safety of others with them
5. Other people not understanding narcolepsy
6. Other people trivializing the impact of narcolepsy
7. Avoiding social interaction and social situations
8. Having difficulty taking care of their homes and families

HCPs and Patients Prioritize Different Challenges of Narcolepsy

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Know Narcolepsy Survey

- Surveyed HCPs* (n=251) cited routines of daily living as being among the biggest challenges facing narcolepsy patients
- Surveyed patients* (n=200) prioritized the emotional challenges of having narcolepsy
- Surveyed patients struggle with others trivializing the disorder
  - 88% of surveyed patients (n=176) agreed that people do not understand how disruptive narcolepsy is to daily life
- 94% of surveyed patients (n=189) agreed that more public education about narcolepsy is needed

The Biggest Challenges of Living With Narcolepsy

	Most frequently cited by HCPs
1	Patients struggle to keep jobs
2	People do not understand what narcolepsy is
3	Patients are unable to complete normal daily tasks
4	Patients worry about their safety or the safety of others with them
5	Patients struggle to get through school

	Most frequently cited by patients
1	People do not understand what narcolepsy is
2	People trivialize narcolepsy and its impact
3	Patients avoid social interaction and social situations
4	It is hard for patients to take care of their homes and families
5	Patients worry about their safety and the safety of others with them

Data on file. Harmony Biosciences. 2018.

*Surveyed HCPs did not necessarily supervise care of surveyed patients.

Question for the Audience

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What percent of your patients with narcolepsy type 1 report avoiding or suppressing emotions as a way to cope with cataplexy?

1. 76-100%
2. 51-75%
3. 26-50%
4. 0-25%

Narcolepsy Can Change the Way Some People Live Their Lives

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Know Narcolepsy Patient Survey

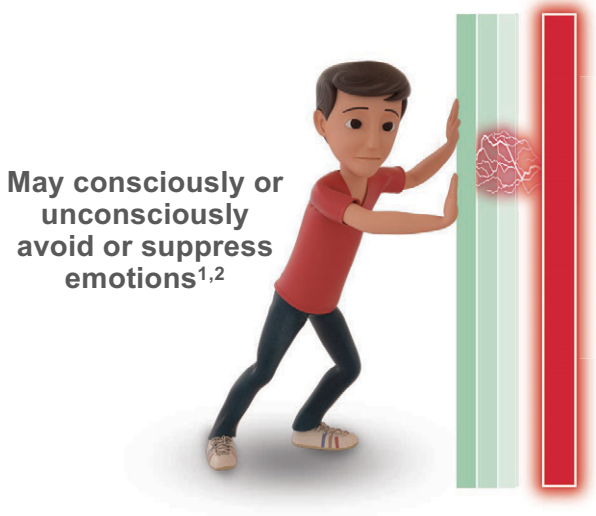
- According to respondents:

86% n=173 Changed their lives in some way because of narcolepsy[1]

28% n=57 Reported suppressing or avoiding emotions[1]

Psychophysiological studies indicate that patients with cataplexy may suppress their own emotions in response to visual stimuli with emotional content[2,3]

Emotional Regulation



1. Data on file. Harmony Biosciences. 2018. **2.** de Zambotti M et al. *J Sleep Res.* 2014;23(4):432-440. **3.** Tucci V et al. *SLEEP.* 2003;26(5):558-564.

Question for the Audience

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Approximately how many days per week would you say narcolepsy disrupts the daily life of your patients or keeps them from being able to do things they wanted to do?

1. 1 day per week
2. 2 days per week
3. 3 days per week
4. 4 days per week
5. 5 days per week
6. 6 days per week
7. 7 days per week

People Living With Narcolepsy May Become Socially Isolated

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Know Narcolepsy Patient Survey

- On average, respondents reported that narcolepsy disrupted their daily life or kept them from being able to do things they wanted to do nearly 4 out of 7 days per week[1]

65% n=130 Reported avoiding activities such as going out[1]

35% n=70 Reported avoiding situations that may trigger symptoms[1]

Social Isolation

May gravitate away from or consciously avoid certain activities[1-3]

1. Data on file. Harmony Biosciences. 2018. **2.** Daniels E et al. *J Sleep Res*. 2001;10(1):75-81. **3.** Ahmed I, Thorpy M. *Clin Chest Med*. 2010;31(2):371-381.

The Psychosocial Impact of Narcolepsy

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- People living with narcolepsy may struggle with social and emotional consequences of their disorder[1,2]
- However, patients may not regularly talk with their HCP about the emotional impact of narcolepsy[3]
- Therefore, it is important to assess the impact of narcolepsy on social functioning and quality of life[1,4,5]

People living with narcolepsy may struggle with:

Social and emotional withdrawal[1,2]

Depressive symptoms[1,2]

Low self-esteem[1]

1. Thorpy M et al. *Sleep Med Clin*. 2017;12(1):61-71. **2.** Overeem S et al. *Sleep Med Clin*. 2012;7(2012):263-281. **3.** Data on file. Harmony Biosciences. 2018.
4. Thorpy M, Dauvilliers Y. *Sleep Med*. 2015;16(1):9-18. **5.** Krahn LE et al. *J Clin Sleep Med*. 2015;11(3):335-355.

Assessing the Social Impact of Narcolepsy

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Ask your patients with narcolepsy…

- Do your narcolepsy symptoms like EDS and cataplexy keep you from doing things you want to do?[1,2]
- Do you avoid emotions or situations that may trigger your symptoms?[1-3]
- Have your narcolepsy symptoms affected your interpersonal relationships?[1-4]
  - ☐ Interacting with friends and family?[1,2]
  - ☐ Making and keeping plans?[5]
  - ☐ Intimate relationships?[3]

1. Maski K et al. *J Clin Sleep Med*. 2017;13(3):419-425. **2.** Broughton R et al. *Can J Neurol Sci.* 1981;8(4):299-304. **3.** Overeem S et al. *Sleep Med Clin*. 2012;7(2012):263-281.
4. Thorpy M, Morse AM. *Sleep Med Clin*. 2017;12(1):61-71. **5.** Daniels E et al. *J Sleep Res*. 2001;10(1):75-81.

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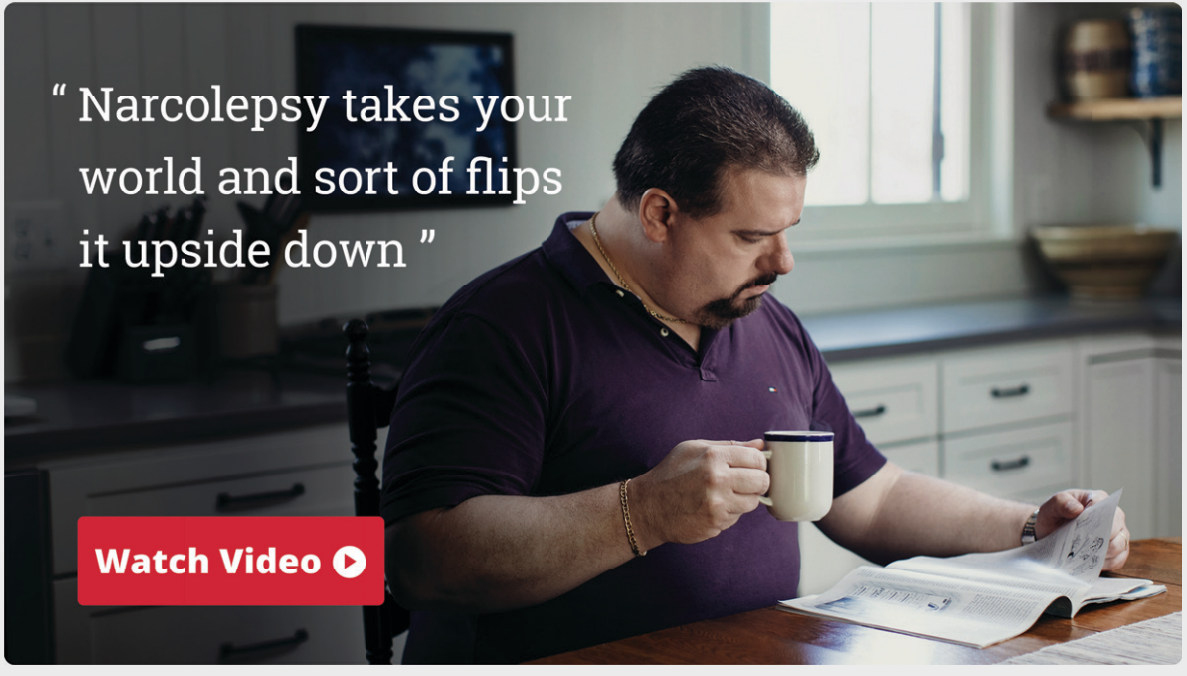
There's More to Know!



Scott

48 years old,
living with narcolepsy
with cataplexy

Question for the Audience

KNOW narcolepsy®

How important is it to assess impairments in psychosocial functioning in narcolepsy?

1. Not at all important
2. A little important
3. Somewhat important
4. Very important

Current Narcolepsy Treatments May Not Be Optimal

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People Living With Narcolepsy

Know Narcolepsy Patient Survey

Although 68% n=137 of all survey respondents said medications have helped them…

93% n=157 of treated respondents expressed frustrations with narcolepsy medications

Nearly all patients surveyed (n=188) agreed we need new treatment options 94% n=188

Eighty-four percent (n=169) of respondents were taking medications for their narcolepsy.

Data on file. Harmony Biosciences. 2018.

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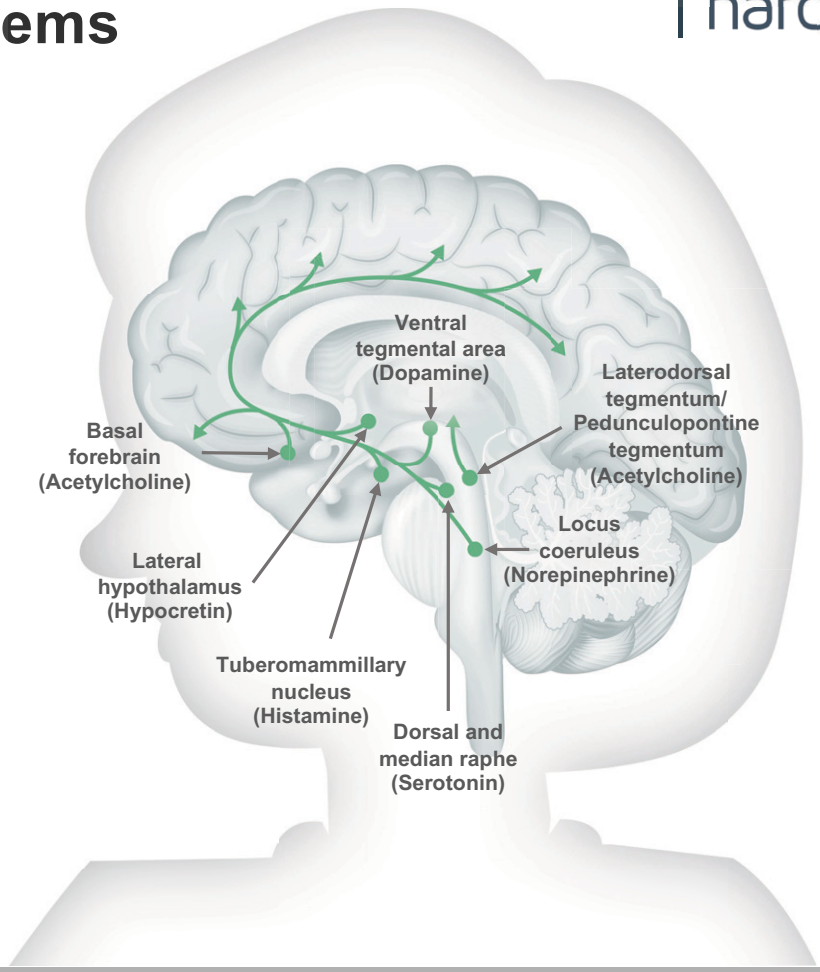
There's More to Know!

The Important Role of Histamine in Sleep-Wake State Stability

Karl Doghramji, MD

Wakefulness Is Promoted by Multiple Wake-Promoting Neuronal Systems

- Wakefulness is promoted by the coordination of interconnected neuronal systems,[1-3] including:
  - Acetylcholine
  - Dopamine
  - Histamine
  - Norepinephrine
  - Serotonin



Adapted with permission from Saper CB et al. *Nature*. 2005;437(7063):1257-1263.

1. Scammell TE et al. *Neuron Rev*. 2017;93(4):747-765. **2.** Saper CB et al. *Nature*. 2005;437(7063):1257-1263. **3.** España RA et al. *Sleep*. 2011;34(7):845-858.

Histamine Is Important for Sleep-Wake State Stability

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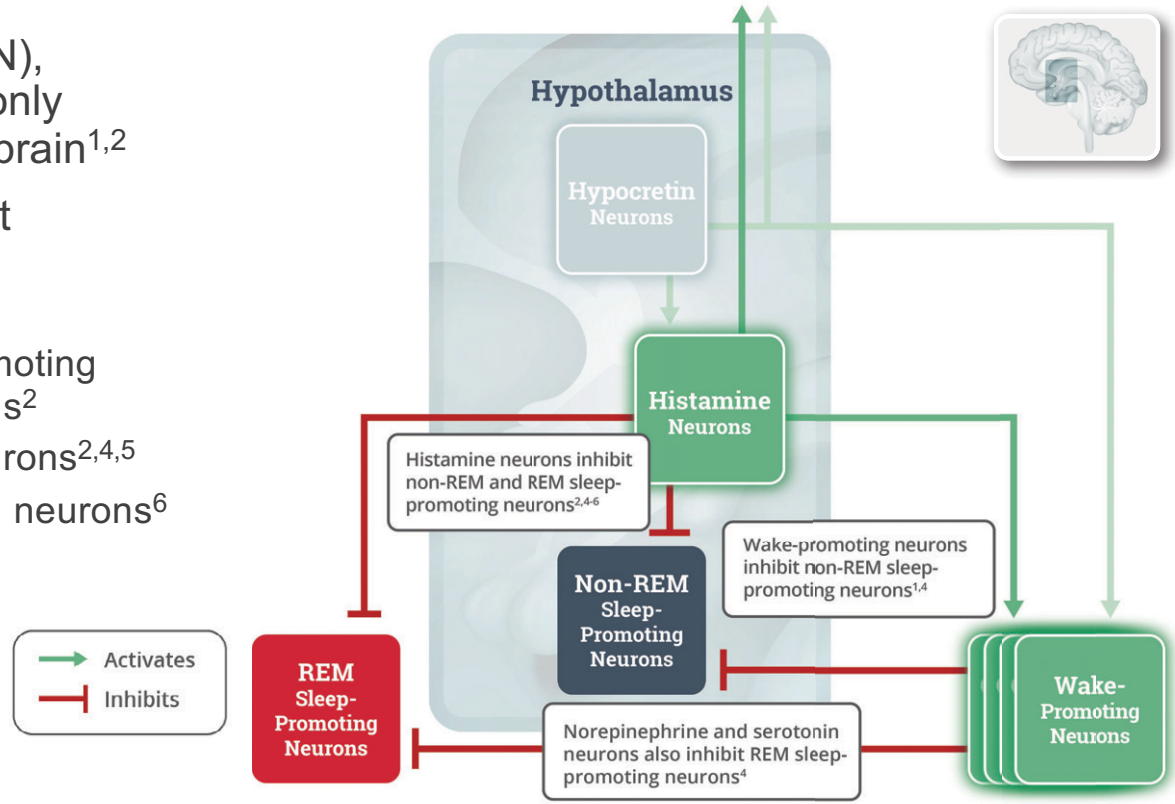
- The tuberomammillary nucleus (TMN), located in the hypothalamus, is the only neuronal source of histamine in the brain[1,2]
- Histamine neurons play an important role in promoting and stabilizing wakefulness[1,3] by:
  - Activating the cortex and wake-promoting neurons outside of the hypothalamus[2]
  - Inhibiting REM sleep-promoting neurons[2,4,5]
  - Inhibiting non-REM sleep promoting neurons[6]



Based on in vitro and in vivo animal studies.

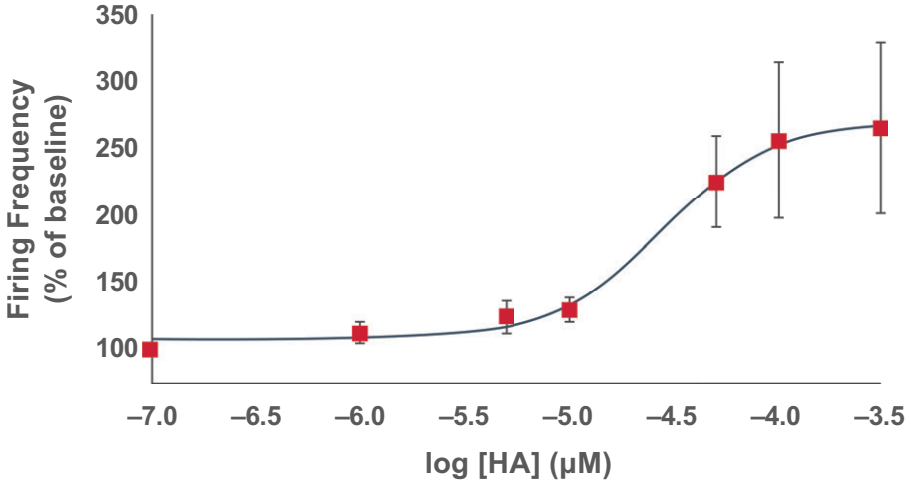
1. España RA et al. *Sleep*. 2011;34(7):845-858. **2.** Haas HL et al. Physiol Rev. 2008;88(3):1183-1241.
3. Parmentier R et al. *J Neurosci*. 2002;22(17):7695-7711. **4.** Scammell TE et al. *Neuron Rev*. 2017;93(4):747-765.
5. Crochet S et al. *Eur J Neurosci*. 2006;24:1404-1412. **6.** Williams RH et al. *J Neurosci*. 2014;34(17):6023-6029.

Histamine Is Important for Sleep-Wake State Stability

Histamine Neurons Promote Wakefulness

- During wakefulness, histamine activates cortical and subcortical neurons[1,2]
- Histamine activates wake-promoting neurons outside of the hypothalamus,[2-4] including:
  - Norepinephrine[2,3]
  - Acetylcholine[2]
  - Serotonin[2]
  - Dopamine[4]
- Activation of norepinephrine neurons is associated with[1]:
  - Increased wakefulness
  - Suppression of REM sleep

Histamine Activates Norepinephrine Neurons in Locus Coeruleus in In Vitro Rat Model[3]



HA, histamine. Single-unit extracellular recording of locus coeruleus neurons isolated from cortical brain slices from 3- to 4-week-old male Wistar rats.[3]

Adapted with permission from Korotkova TM et al. *Neuropharmacology*. 2005;49:129-134.

1. Scammell T et al. *Neuron*. 2017;93(4):747-765. **2.** Haas HL et al. *Physiol Rev*. 2008;88(3):1183-1241. **3.** Korotkova TM et al. *Neuropharmacology*. 2005;49(1):129-134. **4.** Torrealbas F et al. *Front Syst Neurosci*. 2012;6:51.

Histamine Neurons Inhibit Non-REM Sleep–Promoting Neurons

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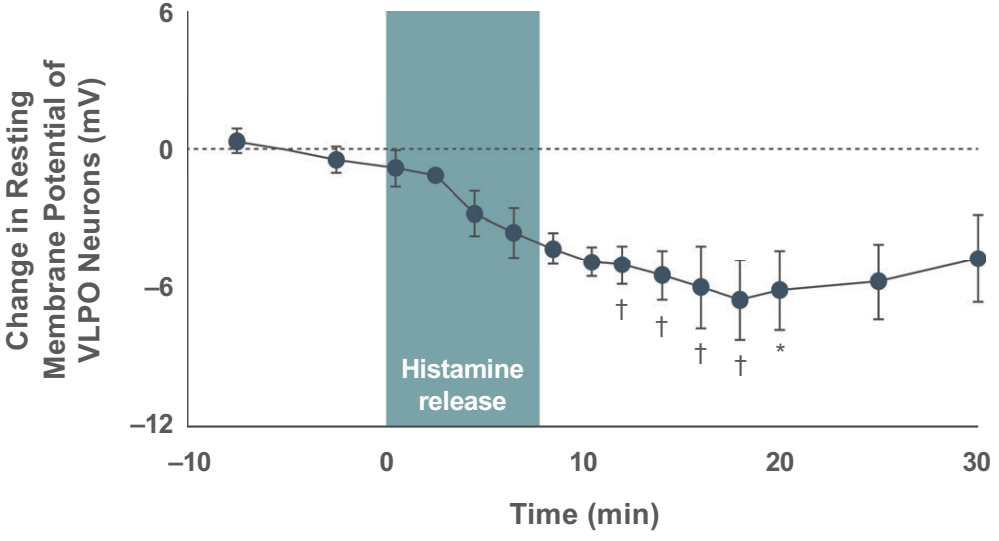
- Histamine inhibits neuronal activity of the ventrolateral preoptic nucleus (VLPO)

Histamine Release Inhibits VLPO Neurons in In Vitro Mouse Model



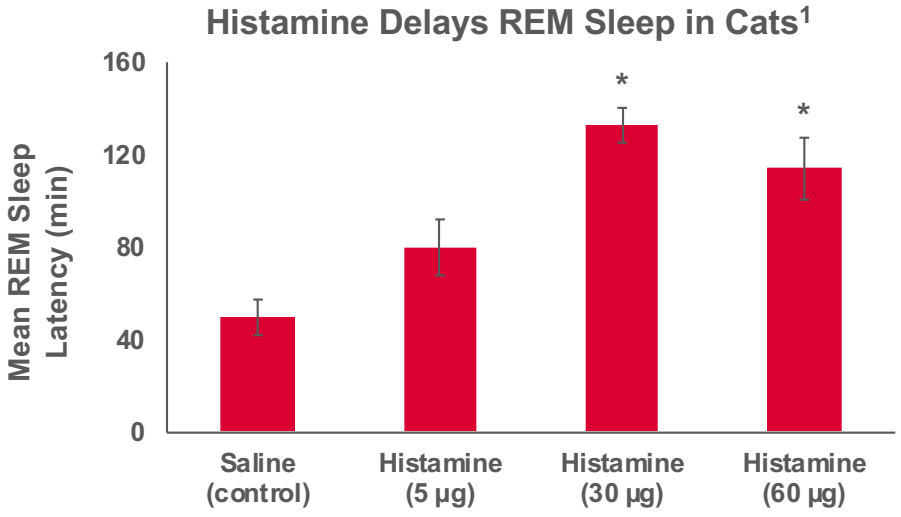
Coronal brain slices obtained from 5-week-old male mice. Patch-clamp recordings obtained from VLPO neurons during photostimulation of channelrhodopsin-2 (ChR2) expressing histamine neurons (n=7). Photostimulation with 3 x 10 ms light pulses over 3 s, repeated every 5 s for 100 trials. *$P<0.05$; †$P<0.01$.

Adapted with permission from Williams RH et al. *J Neurosci.* 2014;34(17):6023-6029.

Williams RH et al. *J Neurosci.* 2014; 34(17):6023-6029.

Histamine Neurons Suppress REM Sleep

- Injections of histamine suppress REM sleep in cats[1]
- Histamine neurons are less active during REM sleep, likely allowing REM sleep to occur[2-4]



Saline (0.9% NaCl, 1 µL) and histamine (5 µg, 30 µg, and 60 µg) were injected into the ventrolateral posterior hypothalamus of adult cats. Polygraphic recordings were carried out for 6 hours. Data represent mean values ± standard error. *$P<0.01$[1]

1. Lin J-S, Sakai K, Jouvet M. *Neuropharmacol.* 1988;27(2):111-122. **2.** Scammell TE et al. *Ann Neurol.* 2003;53(2):154-166.
3. Haas HL et al. *Physiol Rev*. 2008;88(3):1183-1241. **4.** John J et al. *Neuron*. 2004;42(4):619-634.

Histamine Neurons Stabilize Sleep-Wake Transitions

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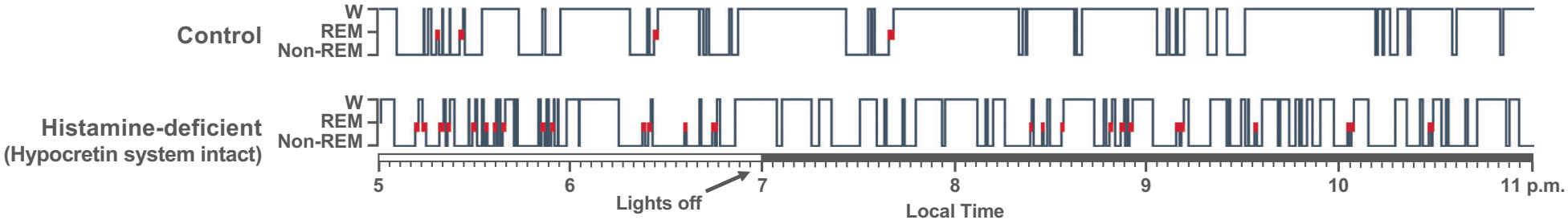
- Mice lacking histamine (with normal levels of hypocretin) have more frequent transitions between sleep-wake states
  - Significant decrease in wakefulness ($P<0.01$) and non-REM sleep episode duration ($P<0.001$)
  - Significant increase in number of wakefulness, REM sleep, and non-REM sleep episodes ($P<0.0001$)

Hypnograms of Histamine-Deficient Mice vs Controls



Typical hypnograms of histamine-deficient mice versus wild-type (control) mice (15 pairs). Histamine-deficient knock-out mice lack histidine decarboxylase (HDC), the sole enzyme responsible for histamine synthesis.

Adapted with permission from Parmentier R et al. *J Neurosci*. 2002;22(17):7695-7711.

Parmentier R et al. *J Neurosci*. 2002;22(17):7695-7711.

Summary

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- Coordinated neuronal systems, including hypocretin and histamine neurons, help ensure stable wakefulness[1-5]
- Narcolepsy is a disorder of sleep-wake state instability characterized by elements of one state intruding into another (e.g., ***REM at the Wrong Time***)[6-8]
- EDS manifestations may be due to insufficient activation of wake-promoting neurons and intermittent activation of non-REM sleep-promoting neurons[1,7-12]
- Elements of REM sleep may intrude into wakefulness and manifest as symptoms of REM sleep dysregulation (e.g., cataplexy, sleep paralysis, and hypnagogic hallucinations)[7,8]
- Narcolepsy symptoms can manifest in many different ways; even less obvious manifestations can have a significant impact on patients' lives[13-16]
- Histamine neurons play an important role in sleep-wake state stability[4,6,17,18]
  - Activate wake-promoting neurons outside of the hypothalamus[4,6]
  - Inhibit REM sleep-promoting neurons[1,19]
  - Inhibit non-REM sleep-promoting neurons[18]

1. Scammell TE et al. *Neuron*. 2017;93(4):747-765. **2.** van der Heide A, Lammers GJ. Narcolepsy. In: Thorpy MJ, Billiard M, eds. *Sleepiness: causes, consequences and treatment*. Cambridge University Press;2011:111-125. **3.** Schwartz MD, Kilduff TS. *Psychiatr Clin North Am*. 2015;38(4):615-644. **4.** Haas HL et al. *Physiol Rev*. 2008;88(3):1183-1241. **5.** Anaclet C et al. J Neurosci. 2009;29(46):14423-14438. **6.** España RA, Scammell TE. *Sleep*. 2011;34(7):845-858. **7.** Scammell TE. *N Engl J Med*. 2015;373(27):2654-2662. **8.** Broughton R et al. *Sleep*. 1986;9(1 Pt 2):205-215. **9.** Aguirre M et al. *Sleep Res*. 1984;13:128. **10.** Saper CB et al. *Neuron*. 2010;68(6):1023-1042. **11.** Saper CB et al. *Nature*. 2005;437(7063):1257-1263. **12.** Chemelli RM et al. *Cell*. 1999;98(4):437-451. **13.** Thorpy M, Morse AM. *Sleep Med Clin*. 2017;12(1):61-71. **14**. Dauvilliers Y et al. *Nat Rev Neurol*. 2014;10(7):386-395. **15**. Daniels E et al. *J Sleep Res*. 2001;10(1):75-81. **16**. Overeem S et al. *Sleep Med*. 2011;12(1):12-18. **17.** Scammell TE et al. *Sleep*. 2019;42(1): doi: 10.1093/sleep/zsy183. **18.** Williams RH et al. *J Neurosci*. 2014;34(17):6023-6029. **19.** Crochet S et al. *Eur J Neurosci*. 2006;24(5):1404-1412.

Question for the Audience

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How important is the role of histamine in promoting and stabilizing wakefulness during the day?

1. Not at all important
2. A little important
3. Somewhat important
4. Very important

Discussion

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Discover more about the impact of narcolepsy and sign up for updates

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