Rethinking Narcolepsy

Exploring unrecognized symptoms and the underlying neuronal processes

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We Need to Think Differently About Narcolepsy

According to respondents of the Know Narcolepsy® Survey:

- **86%** (n=173) of those with narcolepsy have changed their lives because of the disorder
- **38%** (n=77) of those with narcolepsy were misdiagnosed before receiving a diagnosis
- **94%** (n=255) of HCPs agreed there needs to be more public education about narcolepsy

The Know Narcolepsy Survey is a three-party survey of 1,654 US adults including those with narcolepsy (n=200), the general public (n=1,203), and physicians (n=251) currently in clinical practice who have treated patients with narcolepsy in the last two years. The survey was conducted online in March, April and August 2018, respectively, by Versta Research on behalf of Harmony Biosciences, LLC. The Narcolepsy Network collaborated on the patient survey.


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Overview

• The symptoms of narcolepsy
• Wake-promoting neuronal systems in the brain
• Hypocretin and sleep-wake state stability
• The role of histamine in promoting and stabilizing wakefulness
Disclosures

- Harmony Biosciences is the sponsor of this program, and the content of this program was developed by Harmony Biosciences in collaboration with the presenters.
- This is not a continuing medical education (CME) event; therefore, no CME credit will be provided.
- Today’s faculty are paid speakers for Harmony Biosciences.
The Symptoms of Narcolepsy
Question for the Audience

Which of the symptoms below reflect narcolepsy-specific sleep-wake state instability (select all that apply)?

1. Excessive daytime sleepiness (EDS)
2. Sleep disordered breathing
3. Cataplexy
4. Sleep paralysis
5. Hypnagogic hallucinations
6. Mood changes (e.g., anxiety, depression)
7. Disrupted nighttime sleep
Question for the Audience

On a scale of 1 to 5, how important is the role of histamine in promoting and stabilizing wakefulness?

1. Not at all important
2. A little important
3. Somewhat important
4. Very important
5. Extremely important
Narcolepsy Is Characterized by Sleep-Wake State Instability

- People living with narcolepsy experience sleep-wake state instability\(^1,2\)
  - Frequent transitions between sleep-wake states\(^2,3\)
  - Unstable boundaries between sleep-wake states\(^3,4\)


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Narcolepsy Is Characterized by Sleep-Wake State Instability

- Non-REM sleep may intrude into wakefulness as unintended lapses into sleep\(^1,2\)

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Narcolepsy Is Characterized by Sleep-Wake State Instability

- Elements of REM sleep may intrude into wakefulness, manifesting symptoms of REM sleep dysregulation (e.g., cataplexy)\(^1,2\)
- Although rare, a transition to full REM sleep is possible following a cataplexy attack\(^3\)

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Sleep-Wake State Instability Occurs Across 24 Hours


Question for the Audience

In your experience, how long does it take, on average, to receive a narcolepsy diagnosis after symptom onset?

1. 1-3 years
2. 3-5 years
3. 6-10 years
4. More than 10 years
Excessive Daytime Sleepiness May Not Always Be Obvious

**Obvious Manifestations**

**Lapses Into Drowsiness or Sleep**

- Unplanned naps
- Planned naps

**Inability to Stay Awake and Alert Throughout the Day**

- Microsleep episodes
- Automatic behavior
- Impaired executive function

**Impaired Alertness and Neurocognitive Functioning**

- Forgetfulness
- Difficulty concentrating
- Lapses of attention

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Question for the Audience

When evaluating patients for narcolepsy, how often do you ask about the presence of dreams during daytime naps?

1. Always
2. Sometimes
3. Rarely
4. Never
REM Sleep Dysregulation May Manifest in Different Ways

- REM sleep dysregulation may manifest as:
  - Cataplexy\(^1,2\)
  - SOREMPs\(^3\)
  - Hypnagogic/hypnopompic hallucinations\(^3\)
  - Sleep paralysis\(^3\)
  - Vivid dreams\(^4\)
  - REM sleep behavior disorder\(^3\)
  - Dreams during daytime naps\(^5\)
  - Frightening/bizarre dreams\(^4,6\)

SOREMP, sleep onset REM period.

Cataplexy Can Be Difficult to Recognize

**Obvious Manifestations**

**Affecting Most Muscle Groups**

- Knees buckling or collapse to the ground

**Less-Obvious Manifestations**

**Head/Neck Commonly Affected**

- Slurred speech
- Head drops
- Sagging of face or jaw

**Abnormal Muscle Sensations**

- Twitching
- Loss of grip

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Cataplexy Can Be Triggered by a Range of Emotions and Situations

**Emotions**
- Happiness\(^1\)
- Laughter/humor\(^2,3\)
- Anger\(^2\)
- Excitement\(^4\)
- Stress or anxiety\(^2\)
- Tension\(^4\)
- Anticipation\(^2\)
- Embarrassment\(^4\)

**Situations**
- Telling or hearing a joke, making a witty remark\(^2\)
- Being the center of attention\(^2\)
- Unexpectedly encountering a friend or acquaintance\(^2\)
- Being surprised/startled\(^2\)
- Remembering happy events or being emotionally moved\(^4\)
- Sex or romantic moments\(^4\)

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Question for the Audience

Rate the extent to which you agree with the following statement:
People with narcolepsy with cataplexy may suppress emotions or avoid social situations to prevent triggering their cataplexy.

1. Strongly agree
2. Somewhat agree
3. Somewhat disagree
4. Strongly disagree
Sean
33 years old, living with narcolepsy with cataplexy

“ I have to avoid experiencing emotion in order to control my body ”

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Wake-Promoting Neuronal Systems in the Brain
Wakefulness Is Promoted by Multiple Wake-Promoting Neuronal Systems

- Wakefulness is promoted by the coordination of interconnected neuronal systems\(^1\)-\(^3\)
- Several current therapies used to manage narcolepsy symptoms target wake-promoting neuronal systems, including neurons that produce\(^3\),\(^4\):
  - Dopamine (e.g., amphetamines, modafinil)
  - Norepinephrine (e.g., TCAs, SNRIs)
  - Serotonin (e.g., SSRIs)
- Agents that increase dopamine in the nucleus accumbens have potential for abuse\(^5\)

SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.


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Hypocretin, Histamine, and Sleep-Wake State Stability
3 Hs of Sleep-Wake State Stability

• **Hypothalamus**: A critical “control center” in the brain for sleep-wake state stability\(^1\)-\(^4\)
  
  – Contains neuronal systems that help maintain stable wakefulness, including:
    
    - Hypocretin neurons\(^2,5\)
    - Histamine neurons\(^2,6-9\)

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Hypocretin Neurons Promote Stable Wakefulness

- During wakefulness, hypocretin neurons:
  - Activate cortical and subcortical neurons\(^1,2\)
  - Activate histamine and wake-promoting neurons outside of the hypothalamus\(^1,2\)
  - Inhibit REM sleep-promoting neurons\(^1,2\)
  - Inhibit non-REM sleep-promoting neurons\(^1,2\)

Loss of Hypocretin Neurons Leads to Sleep-Wake State Instability

• Lack of hypocretin leads to:
  – Insufficient activation of histamine and wake-promoting neurons outside of the hypothalamus¹
  – Insufficient inhibition of REM sleep-promoting neurons and non-REM sleep-promoting neurons²-⁴

• This process causes sleep-wake state instability³

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The Role of Histamine in Promoting and Stabilizing Wakefulness
Question for the Audience

Regarding the role of histamine in sleep and wakefulness, which of the following are you familiar with? (Select all that apply.)

1. Activation of cortical neurons
2. Activation of wake-promoting neurons
3. Inhibition of non-REM sleep–promoting neurons
4. Inhibition of REM sleep–promoting neurons
5. None of the above
Overview of Histamine in the Brain

- The tuberomammillary nucleus (TMN) is the only neuronal source of histamine in the brain\(^1,2\)
- Histamine neurons help *promote* wakefulness\(^1\) by:
  - Activating the cortex and select wake-promoting neuronal systems outside of the hypothalamus\(^2\)
- Histamine neurons help *stabilize* wakefulness\(^1,3\) by:
  - Inhibiting REM sleep–promoting neurons\(^2,4,5\)
  - Inhibiting non-REM sleep–promoting neurons\(^6\)

A Closer Look at Histamine and Sleep-Wake State Stability

The Role of Histamine in Sleep and Wakefulness

Video available at KnowNarcolepsy.com/hcp
Histamine Neurons Promote Wakefulness
**Promote Wakefulness**

**Histamine Neurons Enhance Cortical Activity**

- Histamine neurons directly activate cortical neurons\(^1,2\)
  - Important for wakefulness and cognitive functions including attention\(^3,4\)
- In mice lacking histamine, cortical EEG during wakefulness showed changes consistent with reduced capacity for attention\(^3\)
- Histamine may be important for initiating wakefulness\(^3,5\)
  - Histamine-deficient mice have notably impaired wakefulness at the start of their active period\(^3,5\)

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EEG, electroencephalography.


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**Promote Wakefulness**

**Histamine Neurons Activate Wake-Promoting Neurons**

- Histamine activates select wake-promoting neuronal systems outside of the hypothalamus,\(^1\)-\(^3\) including:
  - Norepinephrine\(^1,\(^2\)
    - Helps promote wakefulness and suppress REM sleep and non-REM sleep\(^4\)
  - Acetylcholine\(^1\)
    - Helps promote wakefulness and suppress non-REM sleep\(^4,\(^5\)
  - Serotonin\(^1\)
    - Helps suppress REM sleep and non-REM sleep\(^4\)
  - Dopamine\(^3\)
    - Helps promote wakefulness\(^4\)

Based on in vitro and in vivo animal studies.

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Histamine Neurons Stabilize Wakefulness
Stabilize Wakefulness

Histamine Neurons Inhibit Non-REM Sleep–Promoting Neurons

- Histamine inhibits VLPO neuronal activity in vitro\(^1\)
  - This activity is counteracted by a histamine H\(_1\) antagonist

- Following inhibition of histamine neurons during wakefulness, mice rapidly enter non-REM sleep\(^2,3\)

VLPO, ventrolateral preoptic nucleus.

Stabilize Wakefulness

Histamine Neurons Inhibit REM Sleep–Promoting Neurons

- Histamine activates wake-promoting neurons that inhibit REM sleep\(^1,2\):  
  - Norepinephrine neurons  
  - Serotonin neurons
- Infusion of histamine into the viPAG significantly suppressed REM sleep in cats\(^3\)

viPAG, ventrolateral periaqueductal gray


Based on in vitro and in vivo animal studies.
Histamine Is Important for Sustaining Wakefulness

- Mice with disrupted hypocretin signaling have poor maintenance of wakefulness
  - Restoring hypocretin signaling through TMN neurons significantly increases long bouts of wakefulness in these mice

Hypocretin Signaling Through Histamine Neurons Improves Fragmented Wakefulness in Mice

Disruption of hypocretin receptor type 2 (HCRTR2) signaling was achieved a loxP-flanked transcription disrupter (TD) gene cassette that prevents expression of functional HCRTR2. Local expression of HCRTR2 was induced by microinjection of an adeno-associated viral vector (AAV) coding for Cre recombinase. Wakefulness was scored in 10 s epochs and bouts were characterized during the animals’ normal active period (7:00 PM to 7:00 AM).

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Histamine Neurons Stabilize Sleep-Wake Transitions

- Mice lacking histamine have more frequent transitions between sleep-wake states
  - Significantly shorter episodes of wakefulness and non-REM sleep
  - Significantly more bouts of wakefulness, REM sleep, and non-REM sleep

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.
Question for the Audience

On a scale of 1 to 5, how important is the role of histamine in promoting and stabilizing wakefulness?

1. Not at all important
2. A little important
3. Somewhat important
4. Very important
5. Extremely important
Rethinking Narcolepsy Can Help Improve Patient Care

“I feel very comfortable sharing my concerns with my physician.”

Hear how patients prepare for appointments and communicate with their healthcare providers

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Summary

• Sleep-wake state instability manifests as signs and symptoms of narcolepsy\(^1-3\)

• Symptoms of narcolepsy are not always obvious\(^4,5\)

• Neurons in the hypothalamus help stabilize sleep-wake states\(^1,6-8\)

• Like hypocretin, histamine plays an important role in wakefulness\(^1,7-9\)

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Discussion

Discover more about unrecognized manifestations of sleep-wake state instability and sign up for updates

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