

# The Role of Histamine in the Brain

## How does histamine work in the brain?

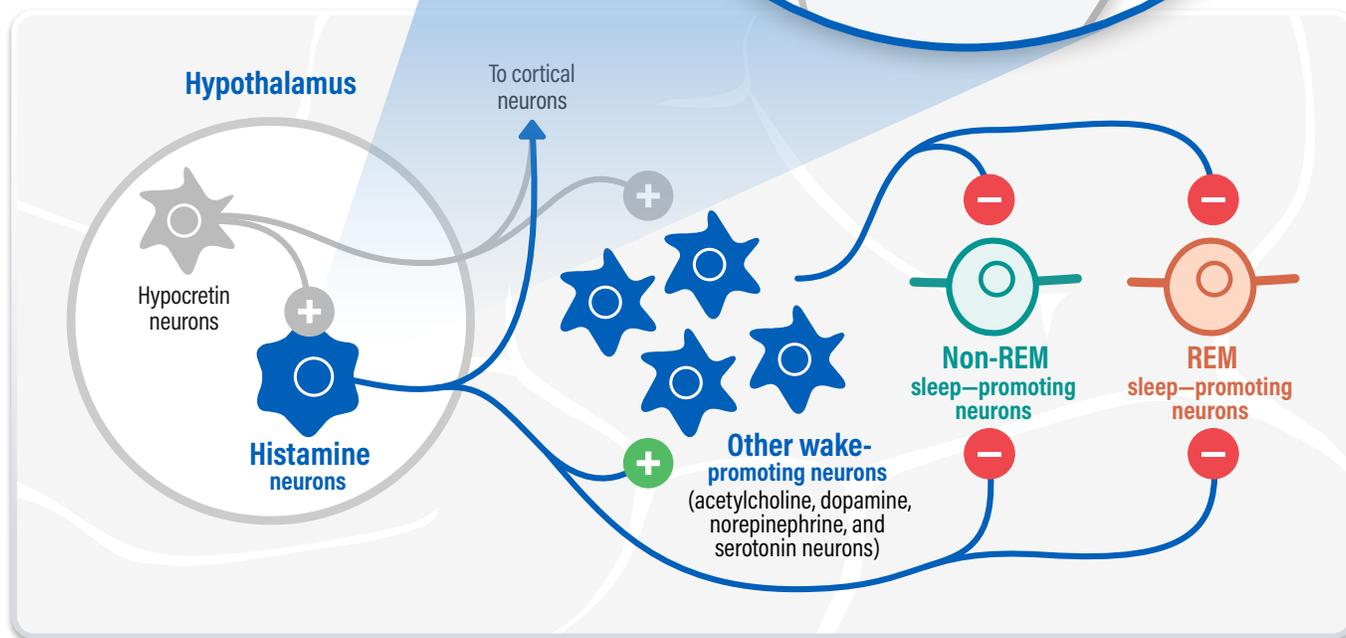
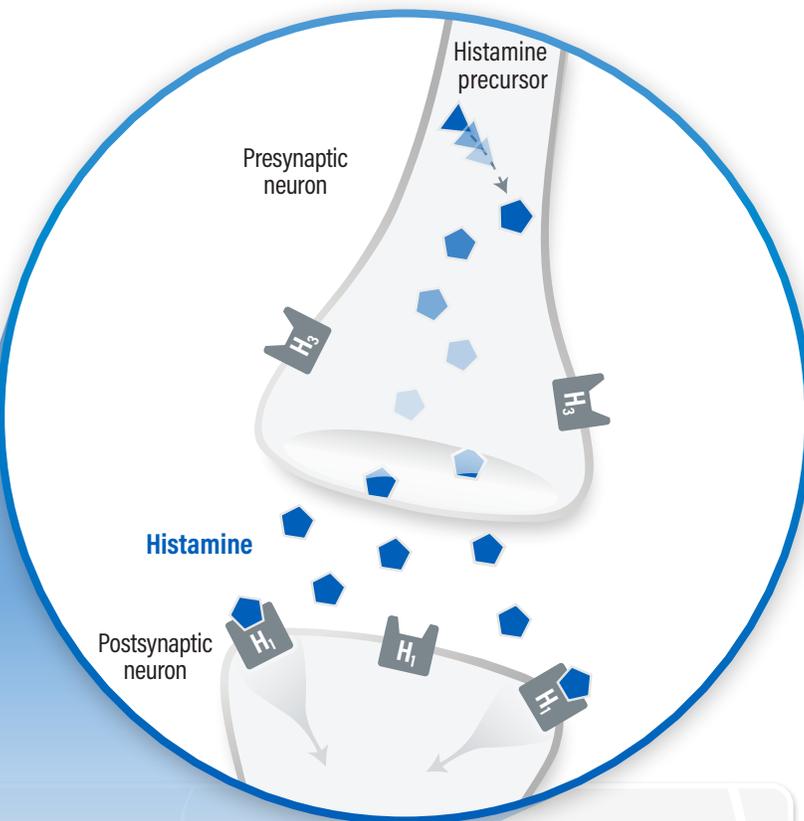
- Histamine is synthesized in the presynaptic neuron<sup>1</sup>
- When released into the synapse, histamine binds to postsynaptic H<sub>1</sub> receptors<sup>1</sup>

## How is histamine activity regulated?

**H<sub>1</sub>** H<sub>1</sub> receptors increase neuronal activity, which allows for communication with important brain regions for sleep and wakefulness<sup>1-3</sup>

**H<sub>3</sub>** H<sub>3</sub> receptors help regulate histamine synthesis and release<sup>4</sup>

- Normally, when histamine levels in the brain are high, histamine binds to H<sub>3</sub> autoreceptors to inhibit further synthesis and release of histamine in the brain<sup>4</sup>



## How does histamine neuron activity promote wakefulness?

**+** Histamine activates wake-promoting neurons<sup>2</sup>

- Cortical neurons
- Other wake-promoting neurons

**-** Histamine inhibits sleep-promoting neurons<sup>1-3</sup>

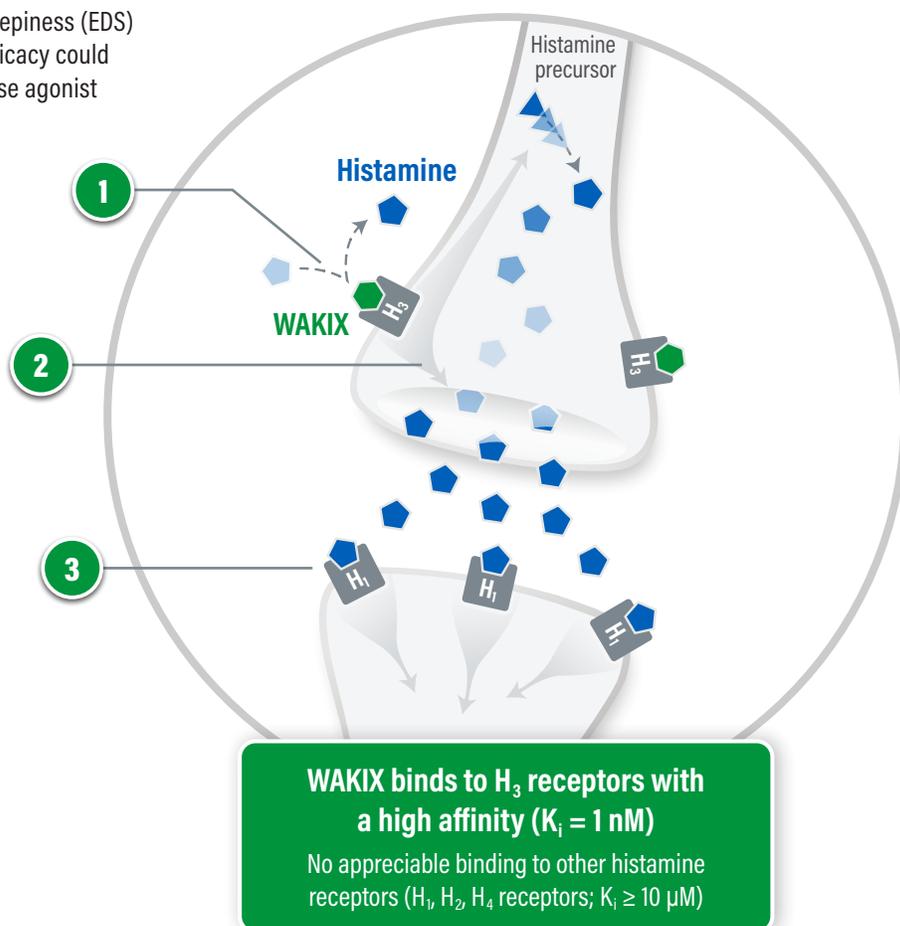
- Non-REM sleep-promoting neurons
- REM sleep-promoting neurons

H<sub>1</sub>, histamine 1; H<sub>3</sub>, histamine 3.

# WAKIX® (pitolisant) Increases Histamine Levels in the Brain

The mechanism of action of WAKIX in excessive daytime sleepiness (EDS) in adult patients with narcolepsy is unclear. However, its efficacy could be mediated through its activity as an antagonist and inverse agonist at H<sub>3</sub> receptors, which results in increased histamine levels in the brain.

- 1 WAKIX blocks histamine from binding to H<sub>3</sub> receptors, which prevents histamine from inhibiting its own synthesis and release (*antagonist effect*)<sup>5</sup>**
- 2 WAKIX produces the opposite effect as histamine by increasing histamine synthesis and its release into the synapse (*inverse agonist effect*)<sup>4-6</sup>**
- 3 Increased histamine in the synapse binds to postsynaptic H<sub>1</sub> receptors, which increases communication to neurons in other brain regions<sup>7,8</sup>**



$K_i$  = inhibitory constant.

## Indications and Usage

- WAKIX is indicated for the treatment of excessive daytime sleepiness (EDS) in adult patients with narcolepsy.

## Important Safety Information

### Contraindications

- WAKIX is contraindicated in patients with severe hepatic impairment.

### Warnings and Precautions

- WAKIX prolongs the QT interval; avoid use of WAKIX in patients with known QT prolongation or in combination with other drugs known to prolong the QT interval. Avoid use in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval.
- The risk of QT prolongation may be greater in patients with hepatic or renal impairment due to higher concentrations of pitolisant; monitor these patients for increased QTc. Dosage modification is recommended in patients with moderate hepatic impairment and moderate or severe renal impairment (see full prescribing information). WAKIX is not recommended in patients with end-stage renal disease (ESRD).

### Adverse Reactions

- In the placebo-controlled clinical trials conducted in patients with narcolepsy with or without cataplexy, the most common adverse reactions ( $\geq 5\%$  and twice placebo) for WAKIX were insomnia (6%), nausea (6%), and anxiety (5%). Other adverse reactions that occurred at  $\geq 2\%$  and more frequently than in patients treated with placebo included headache, upper respiratory infection, musculoskeletal pain, heart rate increased, hallucinations, irritability, abdominal pain, sleep disturbance, decreased appetite, cataplexy, dry mouth, and rash.

Please see Important Safety Information continued on next page and accompanying [Full Prescribing Information](#).

# WAKIX<sup>®</sup> (pitolisant) Is the First and Only Histaminergic Treatment for Patients With Narcolepsy

- First-in-class molecule with a novel mechanism of action
- First and only FDA-approved non-scheduled treatment for patients with narcolepsy
- WAKIX is not a stimulant
- No clinically important pharmacokinetic interactions with modafinil or sodium oxybate
- Convenient once-daily morning dosing

## Indications and Usage

- WAKIX is indicated for the treatment of excessive daytime sleepiness (EDS) in adult patients with narcolepsy.

## Important Safety Information (continued)

### Drug Interactions

- Concomitant administration of WAKIX with strong CYP2D6 inhibitors increases pitolisant exposure by 2.2-fold. Reduce the dose of WAKIX by half.
- Concomitant use of WAKIX with strong CYP3A4 inducers decreases exposure of pitolisant by 50%. Dosage adjustments may be required (see full prescribing information).
- H<sub>1</sub> receptor antagonists that cross the blood-brain barrier may reduce the effectiveness of WAKIX. Patients should avoid centrally acting H<sub>1</sub> receptor antagonists.
- WAKIX is a borderline/weak inducer of CYP3A4. Therefore, reduced effectiveness of sensitive CYP3A4 substrates may occur when used concomitantly with WAKIX. The effectiveness of hormonal contraceptives may be reduced when used with WAKIX and effectiveness may be reduced for 21 days after discontinuation of therapy.

### Use in Specific Populations

- WAKIX may reduce the effectiveness of hormonal contraceptives. Patients using hormonal contraception should be advised to use an alternative non-hormonal contraceptive method during treatment with WAKIX and for at least 21 days after discontinuing treatment.
- There is a pregnancy exposure registry that monitors pregnancy outcomes in women who are exposed to WAKIX during pregnancy. Patients should be encouraged to enroll in the WAKIX pregnancy registry if they become pregnant. To enroll or obtain information from the registry, patients can call 1-800-833-7460.
- The safety and effectiveness of WAKIX have not been established in patients less than 18 years of age.
- WAKIX is extensively metabolized by the liver. WAKIX is contraindicated in patients with severe hepatic impairment. Dosage adjustment is required in patients with moderate hepatic impairment.
- WAKIX is not recommended in patients with end-stage renal disease. Dosage adjustment of WAKIX is recommended in patients with moderate or severe renal impairment.
- Dosage reduction is recommended in patients known to be poor CYP2D6 metabolizers; these patients have higher concentrations of WAKIX than normal CYP2D6 metabolizers.

To report suspected adverse reactions, contact Harmony Biosciences, LLC at 1-800-833-7460 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

Please see accompanying [Full Prescribing Information](#).

Visit [WAKIXhcp.com](http://WAKIXhcp.com) to learn more

### References

1. Scammell TE et al. *Sleep*. 2019;42(1). doi: 10.1093/sleep/zsy183. 2. Haas HL et al. *Physiol Rev*. 2008;88(3):1183-1241. 3. Scammell TE et al. *Neuron*. 2017;93(4):747-765. 4. Nieto-Alamillos G et al. *Mol Pharmacol*. 2016;90(5):649-673. 5. Schwartz JC. *Br J Pharmacol*. 2011;163(4):713-721. 6. Stahl SM. In: *Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 2nd ed. New York, NY: Cambridge University Press;2000:77-98. 7. Lin J-S et al. *J Pharmacol Exp Ther*. 2011;336(1):17-23. 8. Benarroch EE. *Neurology*. 2010;75(16):1472-1479.



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