Scientists Spot Mechanism Behind Promising New Sleep Drug

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An experimental drug called gaboxadol may soon help millions of bleary-eyed insomniacs get to sleep, and a multi-center team of U.S. scientists believes they've pinpointed just how the drug works.

Neuroscientist researchers from Weill Cornell Medical College in New York City; the University of Pittsburgh; and the University of California, Los Angeles, say gaboxadol acts in a whole different way from sleep aids such as Ambien, or older benzodiazepine drugs such as Valium.

What's more, gaboxadol's unique mechanism of action could keep it from disrupting the delicate ratio of REM to non-REM sleep -- a problem plaguing many commercially available sleep aids.

Gaboxadol is currently in Phase III clinical trials as a sleep drug by Merck & Co, in partnership with the Danish company Lundbeck.

"Drugs like Ambien work on the alpha-1 subtype of receptors for the neurotransmitter GABA -- that's akin to an 'on/off switch' for the central nervous system. On the other hand, gaboxadol works on another subtype, called alpha 4 -- it's more of a 'dimmer switch' that might help regulate sleep in a less disruptive way," explains co-researcher Dr. Neil Harrison, Professor of Pharmacology in Anesthesiology at Weill Cornell Medical College.

He and Dr. Gregg Homanics, Associate Professor of Anesthesiology and Pharmacology at the University of Pittsburgh, are co-senior authors on

the paper. Drs. Carolyn Houser, Igor Spiegelman and Richard Olsen of UCLA also contributed to this research.

The findings were published recently in the Proceedings of the National Academy of Sciences.

Each night, millions of Americans struggle with sleeplessness. According to the National Sleep Foundation (NSF), almost six of 10 Americans report having insomnia at least a few nights weekly. As many as 25 percent of people say they have used medications to help them sleep at least once in the past year.

Numerous drugs are available to help people sleep, but nearly all come with undesirable side-effects, such as lingering daytime grogginess.

The search for a drug that might faithfully mimic natural human sleep has led to gaboxadol, which was originally developed in Denmark in the 1970s as a possible anticonvulsant for use in people with epilepsy.

At the time, researchers shelved the drug, noting that it was too sedating.

It was not until the mid-1990s that Dr. Marike Lancel at the Max Planck Institute for Psychiatry in Munich, Germany, revisited gaboxadol as a possible hypnotic, or sleep aid.

"In trials, it does appear to help people get to sleep, although the exact way in which it does so has remained unclear," according to Dr. Harrison.

It appears that, like Ambien, gabodoxal works with GABA, a key central nervous system neurotransmitter that helps inhibit neuronal activity.

However, GABA acts through a variety of receptor subtypes. Ambien

affects the "alpha 1" subunit receptor, through a process called "synaptic inhibition."

Gaboxadol does not appear to work in this way, however.

In their study, Dr. Harrison joined up with researchers at U. Pitt and UCLA to determine the drug's precise mechanism of action.

First, they turned to U. Pitt graduate student Dev Chandra, who genetically engineered a "knockout" mouse that lacked another key GABA subunit, called alpha 4.

"The alpha 4 subunit is expressed at high levels in the thalamus -- a key neurological 'sleep center' -- so we suspected it might play a role," Dr. Harrison explains.

In their experiments, normal mice became sedated when exposed to gaboxadol. However, mice that lacked the alpha 4 subunit remained awake and unaffected by the drug.

"That tells us that the drug needs this subunit in order to work," Dr. Harrison says.

It also suggests that, unlike Ambien, gaboxadol doesn't trigger sleep by the blunt 'on/off' mechanism of synaptic inhibition.

"Synaptic inhibition via the alpha 1 subunit simply gets neurons to stop firing," Dr. Harrison explains.

"On the other hand, compounds that affect the alpha 4 subunit act like a 'dimmer switch' -- down-regulating neuronal activity in the thalamus," he says.

The thalamus is the last key regulator of activity in the cerebral cortex, and is needed for sleep. According to previous work done by Dr. Fan Jia and Dr. Harrison with Dr. Peter Goldstein at Weill Cornell, gaboxadol selectively activates receptors in the thalamus with the alpha 4 subunit, which, in turn, may cause specific neurons in the thalamus to begin firing at a very slow, regular rhythm.

"It's this pattern of firing that helps send our brains into restful, slow-wave sleep," Dr. Harrison explains.

This more subtle, gradual reduction in neuronal firing works outside the synapse and is called tonic inhibition.

"We need more in-depth study to prove all this, but we think this is how gaboxadol is working," Dr. Harrison says. "If so, it would be the first case where a sleep aid has made use of an extra-synaptic receptor like alpha 4."

In fact, preliminary research suggests that this type of tonic inhibition may occur naturally.

"In other words, this drug may simply be replicating what goes on in healthy brains," Dr. Harrison says. That's important, he says, because the ideal sleep drug would mimic natural sleep processes -- offering users quick, uninterrupted sleep; a good balance between REM and non-REM sleep states; and a refreshed, non-drowsy feeling upon awakening.

"So far, it appears that gaboxadol may satisfy all those criteria," Dr. Harrison says.

This study received no private finding. The mouse model used in the study was developed with funding from the U.S. National Institutes of Health.

Other co-authors include Dr. Fan Jia of Weill Cornell Medical College, New York City; J. Liang and A. Suryanarayanan of the University of California, Los Angeles; and D.F. Werner of the University of Pittsburgh.

Source: NewYork-Presbyterian Hospital