

**NEWS**

# Melatonin gains momentum as sleep aid for people with autism

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Most people with autism have problems falling and staying asleep. And poor sleep can exacerbate behavioral problems, leaving these individuals — and their families — exhausted.

The hormone melatonin, sold in the United States as an over-the-counter supplement, is a popular sleep aid. A string of studies over the past decade suggest it also improves sleep in some children with autism. And a new formulation of melatonin seems to be particularly effective for children on the spectrum.

Melatonin is naturally produced by the body to regulate the sleep-wake cycle. Its levels begin to rise shortly after nightfall, promoting sleep.

Most of the studies supporting its use in autism have included only a few dozen children<sup>1,2</sup>. But in one study of 134 children with autism, melatonin improved sleep in 63 percent of the children who received it. It was particularly effective when combined with behavioral treatment<sup>3</sup>.

In November, researchers published results from a clinical trial of 125 children with autism for a new melatonin product<sup>4</sup>. Called PedPRM, the pills release melatonin slowly into the bloodstream, and represent the first melatonin formulation developed by a pharmaceutical company. The pill helped 38 of the 56 children who received it fall asleep faster and stay asleep longer. (The other 61 children took a placebo, and 12 of them showed improvement.)

“This is a formulation that was found to be effective in helping insomnia in children with autism,” says lead researcher **Robert Findling**, vice president of psychiatric services and research at the Kennedy Krieger Institute in Baltimore.

These studies and anecdotal reports suggest that a significant subset of children with autism could benefit from taking melatonin. But the current trial-and-error approach to identifying these children is not ideal.

“It would be great if ultimately we could figure out which kids are going to be responsive to melatonin versus which ones are going to need stronger medications,” says **Beth Malow**, professor of neurology and pediatrics at Vanderbilt University in Nashville, Tennessee.

### **Precise dose:**

When sleep problems surface, doctors generally prescribe behavioral strategies first. For example, they may urge people on the spectrum to follow a bedtime routine, or to avoid stimulating drinks, video games and television close to bedtime.

If these tactics don't work, they may suggest adding melatonin to the mix.

Malow recommends starting with a 1 milligram tablet and going up to 3 milligrams if the child doesn't improve. Doctors should also consider other factors, such as gastrointestinal problems or anxiety, that might disrupt a child's sleep.

Although melatonin itself is generally safe, it's not always clear what the pills sold in shops contain<sup>5</sup>. Because melatonin is considered a supplement rather than a drug, the U.S. Food and Drug Administration (FDA) does not regulate the quality of the pills that claim to contain the hormone.

A study published earlier this year analyzed 31 such supplements and found that two out of three did not match the dosage on their labels<sup>6</sup>. Some brands contained less than one-fifth of the advertised dose, and others contained four times more. Some also contained the **neurotransmitter** serotonin, which is toxic at high doses.

"The supplements tend to be quite imprecise in terms of the dosage, and we can't be sure what's in them," says **Craig Canapari**, a pediatric sleep specialist and director of the Yale Sleep Medicine Program. "My patients ask which brands they should take, and I tell them I have no idea."

The new pill may address this pitfall. Made by **Neurim Pharmaceuticals**, based in Israel, the tiny pill contains a precise dose of the hormone and is easy for children to swallow.

The slow-release formulation mimics the way the body secretes melatonin into the bloodstream, says **Olivia Veatch**, a research fellow at the Center for Sleep and Circadian Neurobiology at the University of Pennsylvania, who was not involved in the trial. "While a single-release melatonin may help someone to fall asleep more quickly, prolonged release is more likely to help someone stay asleep throughout the night," she says.

After 13 weeks of treatment, children who received the pill slept, on average, an hour longer than they used to. They also fell asleep an average of about 40 minutes faster.

"One more hour of sleep is a pretty significant outcome," Canapari says. "Looking at a result like this, I would absolutely consider prescribing this for my patients if their insurance would cover it."

## Biological basis:

All studies of melatonin to date show that only some children respond to it. Some doctors, such as Canapari, believe there is little harm in people trying it to see if it works for them. But understanding how different people process melatonin might eventually lead to a way of predicting who would benefit from it.

Sleep problems can arise from low levels of melatonin. Some people with autism carry **mutations in an enzyme** involved in melatonin production. Supplements containing melatonin may increase the levels of the hormone in these individuals.

For example, four children in the new trial have Smith-Magenis syndrome, a rare condition related to autism. There is some evidence suggesting that people with the syndrome have **an inverted**

**melatonin rhythm** — meaning melatonin is at peak levels during the day as opposed to at night<sup>7</sup>. That may explain why these children responded as well as they did to the pill, says Veatch.

“It is definitely likely that supplemental melatonin is treating a deficiency in endogenous melatonin production during the night in this population,” she says.

Evidence for low levels of melatonin in other children with autism is mixed: A 2012 study suggested that teenagers with autism have less melatonin in their urine than typical teenagers do during the day and night<sup>8</sup>. But two years later, another study reported no difference in melatonin levels between children with autism and controls<sup>9</sup>.

“I think a lot more needs to be done in terms of the melatonin deficiency question,” Malow says. “I think it's a jump to conclude there's a melatonin deficiency.”

Neurim Pharmaceuticals is taking steps toward gaining FDA approval for the pill.

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