



Shift workers have a higher risk of depression, possibly because of misaligned body clocks.

Sadness and schedules

Disrupted sleep and unnatural light exposure might increase the risk of depression. Understanding how could help to mitigate the risk. **By Sarah DeWeerd**

Between 2015 and 2018, researchers invited 23 people to a laboratory at Brigham and Women's Hospital in Boston, Massachusetts, for a study of the body's daily cycles, known as circadian rhythms. During one phase of the experiment, the study participants kept to a fairly typical night-time sleep schedule. In another phase, the researchers reversed the participants' sleep-wake cycle in a procedure that was designed to mimic the experience of night-shift workers.

"Epidemiological studies suggest that night-shift workers are at [approximately] 25% to 40% higher risk for mental illnesses, including depression and anxiety," says Sarah Chellappa, a neuroscientist at the University of Cologne in Germany. Chellappa and her collaborators wanted to understand why. In both parts of the experiment, participants completed a computerized questionnaire about their mood several times a day. When the researchers implemented the schedule switch, participants' mood plummeted, and failed to improve during the four days they spent on the reversed schedule¹.

The findings suggested that one reason for an increased risk of depression among shift workers is the misalignment of the body's internal clock with the outside world.

Up to one in five people in industrialized countries are shift workers², and the study participants included individuals who worked nights, as well as those who worked day shifts. People in both groups experienced a darkening of mood when their schedules were knocked out of whack – an indication that circadian misalignment has negative effects even on long-time shift workers. "This is not just some academic question," says Frank Scheer, a chronobiologist at Harvard Medical School in Boston and Chellappa's collaborator on the study of circadian misalignment. "It's something that's of relevance to one of the most vulnerable populations" of workers.

Much of the public conversation around depression casts the disease as a chemical imbalance in the brain. But mood disorders have increased with modern lifestyles. There is growing evidence that circadian-rhythm disruptions and altered light exposure² (with

more artificial light at night and less natural daylight during the day) that accompany those lifestyles increase the risk of depression.

"Our modern environment is not really great for our circadian clock," says Colleen McClung, a chronobiologist at the University of Pittsburgh in Pennsylvania. "This is an ancient mechanism in our brains and our bodies that evolved at the very beginning of life on Earth, and now we have the ability to have electric lights and to fly across time zones and work late at night. And our biology has not caught up to that at all."

Scientists have known for decades that sleep problems and circadian disruption are associated with depression. The cause-and-effect relationships between these factors have been difficult to tease apart. But, as the links become clearer, more attention is turning to non-pharmacological therapies that modulate sleep and circadian rhythms – sometimes known as chronotherapeutics – as treatments for depression. Some researchers are even investigating the possibility of delivering circadian-rhythm modulation in a pill. Others are exploring ways to tweak the details of modern life to reduce the risk of depression, particularly for shift workers.

Light and shadow

According to one study, more than 90% of people with depression have sleep problems³, and sleeping too much or too little is one of the diagnostic criteria for depression. In the past decade, multiple studies have tracked people's sleep habits and mental health over time and have shown that sleep difficulties at a certain time point increase the likelihood that a person will develop depression later in life. Poor sleep turns out to be not only a symptom but also a predictor.

Fortunately, psychologists have an arsenal of behavioural interventions that can improve sleep, says Aliza Werner-Seidler, a clinical psychologist at the Black Dog Institute at the University of New South Wales in Sydney, Australia. These interventions frequently help people to sleep better and can also ease depression symptoms. "If a client was sitting in front of me with significant sleep problems and significant mental-health problems, and didn't have a preference on where to start, I would definitely be going down the sleep problem route," says Werner-Seidler.

What's more, sleep has a protective effect: improving sleep can help to prevent depression in adults. Werner-Seidler is now wrapping up a study to test whether a sleep intervention delivered through an app can stave off the development of symptoms of mental illness in adolescents aged 12–16 with sleep problems⁴; preliminary results are promising, she says. She

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is working with more than 20 schools in New South Wales to help improve student sleep.

Another non-pharmaceutical approach to treating depression involves the manipulation of light, one of the strongest influences on the circadian system that keeps the body's internal clock in synch with the environment. Studies over the past decade have shown that light also has a direct antidepressant effect, through the stimulation of mood-regulating brain centres.

Spending 30 minutes in front of a source of bright, full-spectrum light in the morning is well established as a treatment for seasonal depression. But the use of light therapy for other forms of depression has been slower to develop, says Christian Cajochen, head of the Centre for Chronobiology at the University of Basel in Switzerland.

Early studies of light therapy for non-seasonal depression reported mixed results – but in the past decade, researchers have begun to take a second look. A 2016 study showed that the antidepressant fluoxetine plus bright light therapy provides more consistent relief from non-seasonal depression than either treatment alone⁵. And in July, a group of researchers including Cajochen reported results from a study of people with perinatal depression that suggest light therapy can help these patients as well⁶. Although best used in conjunction with pharmaceutical antidepressants, light is “as potent as antidepressant drugs”, Cajochen says.

Circadian target

In some cases, a more radical overhaul of the body's circadian rhythms might be necessary to treat depression. In the early 1970s, researchers realized that keeping people with depression awake for 36 hours often provided immediate relief of their symptoms. As a research assistant on a ward for people with severe depression in 1975 at the US National Institute of Mental Health in Bethesda, Maryland, Blynn Bunney, now a biological psychologist at the University of California, Irvine, recalls witnessing effects of sleep deprivation that were nothing short of “miraculous”.

But such patients generally saw their symptoms return after a good night's sleep – a big problem for actually implementing sleep deprivation as a treatment for depression. Later studies showed that this relapse could be prevented by combining sleep deprivation with light therapy and what researchers call sleep phase advance – essentially, going to bed earlier. In a 2009 study, a group including Bunney showed that half of people who underwent this routine remained in remission after seven weeks⁷.

Sleep deprivation, also known as wake therapy, is now used in some European countries.



A volunteer ahead of a night at a sleep lab.

Although the intervention is brief, it's intense – staff must work to keep people awake – and until recently it has been studied mostly in in-patient settings. But a pilot study published in 2021 showed that the approach could be adapted to help people who are not hospitalized⁸, raising the prospect of much wider use.

The increased focus on the importance of the circadian system in depression has also spurred a search for drugs that can alter or strengthen circadian rhythms. Such medication could be used as an alternative or add-on treatment to conventional antidepressants or as mood stabilizers in bipolar disorder – a condition characterized by extreme mood swings.

Two of the most important existing treatments for bipolar disorder, lithium and valproic acid, both affect circadian rhythms, says McClung, who has studied other circadian-modulating compounds in a mouse model of bipolar disorder. And in mouse brains, sleep deprivation and the rapid-acting antidepressant ketamine both cause similar changes in the expression of circadian-related genes⁹. This provides a hint that the circadian system might be especially relevant to the search for compounds that can provide fast relief from depression symptoms.

But drugs that can get into the brain without causing other side effects have proved elusive. For example, agomelatine, a compound related to melatonin, a hormone involved in the sleep-wake cycle, is approved as an add-on treatment for depression in Europe and Australia. But phase III trials in the United States showed weak results and possible liver toxicity.

Lifestyle changes

If elements of modern life increase the risk for depression, what about tweaking modern life to be friendlier to mental health? Such changes could help shift workers and others alike. For example, Chellappa and Scheer have unpublished data showing that eating in synch

with typical mealtimes, even if a person's sleep schedule is altered, can prevent the adverse effects of circadian disruption on mood. This might be a tricky strategy for shift workers to implement, given all the other constraints on their schedules. But it could be used to help fight jet lag and other circadian disruptions that are prevalent in modern life, the researchers say.

Another approach might be to redesign evening lighting in homes or night-shift lighting in factories so that it doesn't affect the body's internal clock. The circadian system responds most strongly to blue light at wavelengths of around 480 nanometres. Taking advantage of LED technology, researchers can create light spectra that exclude these wavelengths but otherwise look normal to the human eye.

However, it's much easier to implement such lighting on a flat computer screen or electronic display than in overhead or ambient lighting, says Manuel Spitschan, a visual neuroscientist and chronobiologist at the Max Planck Institute in Tübingen, Germany. Using room lighting that makes a blank piece of paper appear reassuringly white might make a person's skin look grey – and that uncanny appearance of the world might have its own psychological effects.

Excluding those doing shift work, many people might be able to moderate the mood-altering effects of modern life on the circadian system by changing their behaviour rather than changing technology, Spitschan argues. He was part of an international team of scientists that earlier this year released recommendations¹⁰ for better ‘light hygiene’, such as getting outside during the morning and limiting artificial light in the hours before bed in the evening. Refining such recommendations will require studies that reflect the light exposures people actually experience in their everyday lives, rather than the extreme conditions of lab studies, Spitschan cautions. Still, it's an empowering thought: “We're not lab rats,” he says. “We don't just sit in a shoebox and someone else changes the lighting.”

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