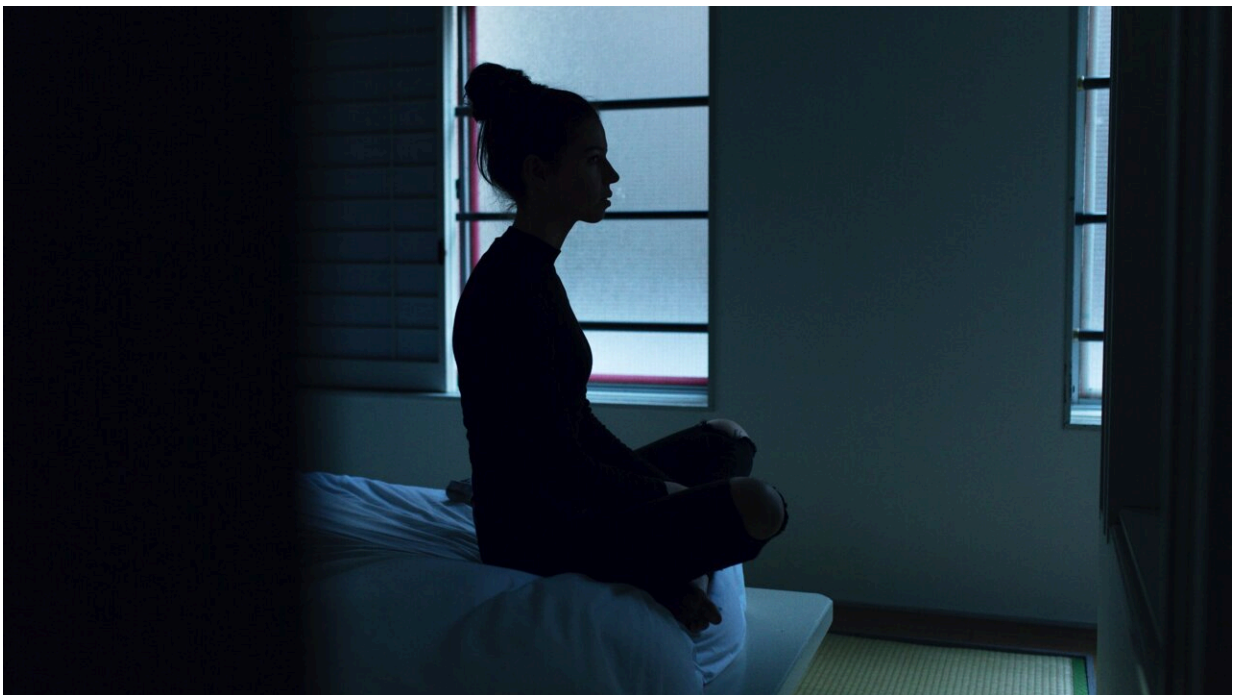


# Antipsychotic medication clozapine linked to significantly less insomnia in people with schizophrenia

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Insomnia affects up to half of people with schizophrenia and is thought to worsen the impact of their disease, including their risk of suicide. A new meta-analysis of the antipsychotics these patients take indicates those who take clozapine have significantly fewer problems with

insomnia, investigators report.

Insomnia and suicide risk have been linked in [schizophrenia](#), and clozapine is the only antipsychotic with a Food and Drug Administration indicator for reducing suicide risk, says Brian Miller, MD, psychiatrist and schizophrenia expert at the Medical College of Georgia at Augusta University.

MCG investigators say it's plausible that clozapine's ability to essentially double [patients'](#) ability to sleep versus other antipsychotics helps explain the reduced suicide risk. Insomnia has been found to generally worsen schizophrenia symptoms and complications from obesity to depression.

However, clozapine, which has a small risk of big side effects including inflammation of the heart muscle and an acute, severe drop in [immune cells](#) that can leave patients vulnerable to life-threatening infections, is typically only used in patients with treatment-resistant schizophrenia, not as a first-line therapy, says Miller, who has dozens of these patients taking clozapine.

The MCG investigators performed what appears to be the first systematic review of [insomnia](#) in patients with schizophrenia that looked at the impact of clozapine versus other antipsychotics. They reviewed information on 1,952 patients enrolled in eight [clinical trials](#) that included 922 people treated with clozapine and the remainder with other first-line antipsychotics, like risperidone and olanzapine.

They found each of the other antipsychotics associated with increased odds of having insomnia compared to clozapine; overall a 2.2-fold increased risk.

Their findings published in the journal *Schizophrenia Research*, support and extend previous work indicating clozapine can help combat insomnia

in these individuals, says the study's senior author Vaughn McCall, MD, an expert in the trifecta of insomnia, depression and suicide who chairs the MCG Department of Psychiatry and Health Behavior.

While all the connections have not been made, there is no question that, bigger picture, the inability to sleep can make you desperate and become a recipe for disaster, McCall says. In fact, multiple studies by experts like McCall have associated insomnia and suicide outside of schizophrenia.

Either way, a bottom line of the new study is that physicians need to be aggressive in assessing and treating insomnia in patients with schizophrenia, says corresponding author Miller. With close monitoring, clozapine may be an answer for some, they say.

"This is a drug with dramatic upsides and dramatic downsides," McCall says. "It is not a trivial decision to use this drug."

"But one of its tremendous upsides is the FDA's indication for suicide prevention," adds Miller, which again likely links back to the drug's efficacy in insomnia. Clozapine also has been associated with increased total sleep time and efficiency.

One quarter to one half of patients with schizophrenia and related problems have ongoing issues with insomnia, Miller says, which may continue despite treatment with an antipsychotic. Clozapine is typically used in patients in whom two other antipsychotics have been tried and failed to control their schizophrenia.

"We use it because it changes lives," Miller says. He notes some of his patients who have dropped out of college because of their illness, go back to school, get good jobs, some have even completed graduate school on clozapine. Miller noted a patient he met during his fellowship

training at MCG and AU Health who had been hospitalized nine times in a single year. On clozapine, the patient was hospitalized once or twice in a decade, both times triggered by a urinary tract infection, Miller says.

"I just think that when you are not sleeping well, whether it's because of symptoms of a psychiatric illness, or because you have a newborn child or for whatever reason you got a bad night's sleep, the world is just not the same the next day," Miller says. "If you have that start stacking on itself, cumulatively the effects could be substantial."

The investigators write that clozapine's association with decreased suicide risk is likely "complex and multifactorial," that published reports are relatively few and a better understanding of the association with insomnia is needed. There are likely multiple factors including genetics at play plus the symptoms of the condition itself, they say.

"If you are hearing voices that are unrelenting, if you are suspicious or paranoid that someone is out to harm you, it makes it really hard to sleep," Miller says. Patients also may self-medicate with caffeine to try to address often significant symptoms like attention problems.

Miller says one theory about how clozapine may combat insomnia is it acts on multiple different receptors in the brain to change the message neurons send. He often uses the Goldilocks analogy that the combination of receptors where it acts is "just right."

Variations in the receptor for melatonin, a hormone that helps regulate the sleep-wake cycle, have been associated with insomnia in schizophrenia. As with many of us, insomnia is associated with other negative health issues like night eating and obesity as well as higher blood levels of fat and cholesterol in people with schizophrenia.

McCall and Miller theorize that the strong antihistamine effect of

clozapine may contribute to its impact on both insomnia and suicide. Histamine is a chemical produced by the immune system in response to an invader such as an allergen like ragweed or cat dander. But too much histamine can also cause a host of problems from congestion to itchy skin to a runny nose and insomnia. There is evidence that histamine signals the brain to stay awake, one reason the antihistamines we take for a runny nose can also make us sleepy. Miller notes that while all antipsychotics block histamine, clozapine is the most potent.

Clozapine's severe potential side effects include agranulocytosis, the condition which can leave you vulnerable to life-threatening infections; the heart muscle inflammation called myocarditis; seizures; a pulmonary embolism; and metabolic syndrome including significant weight gain. Miller referenced one of his patients who gained 30 pounds in just six weeks on clozapine.

Miller notes that the actual risk of some of these serious side effects, like agranulocytosis, is low, about 1%, but real and requires a weekly blood test for the first six months of treatment and close follow up after that.

The drug also has many benefits in addition to reducing suicide and insomnia risk, including a lower risk of the potentially irreversible movement disorder tardive dyskinesia than some other antipsychotics, improving cognition, which can be significantly impacted with schizophrenia, impairing the ability to work and live independently and fewer relapses.

There are a very limited number of patients who can ultimately reduce how much clozapine they take and/or eventually stop taking other antipsychotics but overall their experience with weaning has not gone well, Miller says.

McCall notes that the opportunity to "rescue" a patient a second time with antipsychotics is less than with their initial experience. However, when there are those catastrophic consequences like heart failure, you have to at least change the drug, McCall says.

Oddly, they also found that quetiapine, an antipsychotic often given off label for insomnia, had the highest odds of insomnia risk compared to [clozapine](#), they report. Also oddly, other trials have failed to show quetiapine's benefit on a good night's sleep other than in schizophrenia.

Despite the associated concerns, McCall notes that insomnia is not included as a core symptom of schizophrenia, in the Diagnostic and Statistical Manual of Mental Disorders.

McCall and Miller have been collaborating for about five years to learn and publish more about sleep and suicide in psychiatric and mood disorders. Objective clues to assess [suicide risk](#) could be beneficial, and their current pursuits include, much like an ophthalmologist might, seeing how the pupils respond to light to determine if a state of hyperarousal reflects these often related risks in patients with schizophrenia.

**More information:** Brian J. Miller et al, Meta-analysis of clozapine and insomnia in schizophrenia, *Schizophrenia Research* (2023). [DOI: 10.1016/j.schres.2023.01.018](https://doi.org/10.1016/j.schres.2023.01.018)

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