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Suicide-risk warning on anti-seizure medications lacks evidence: study

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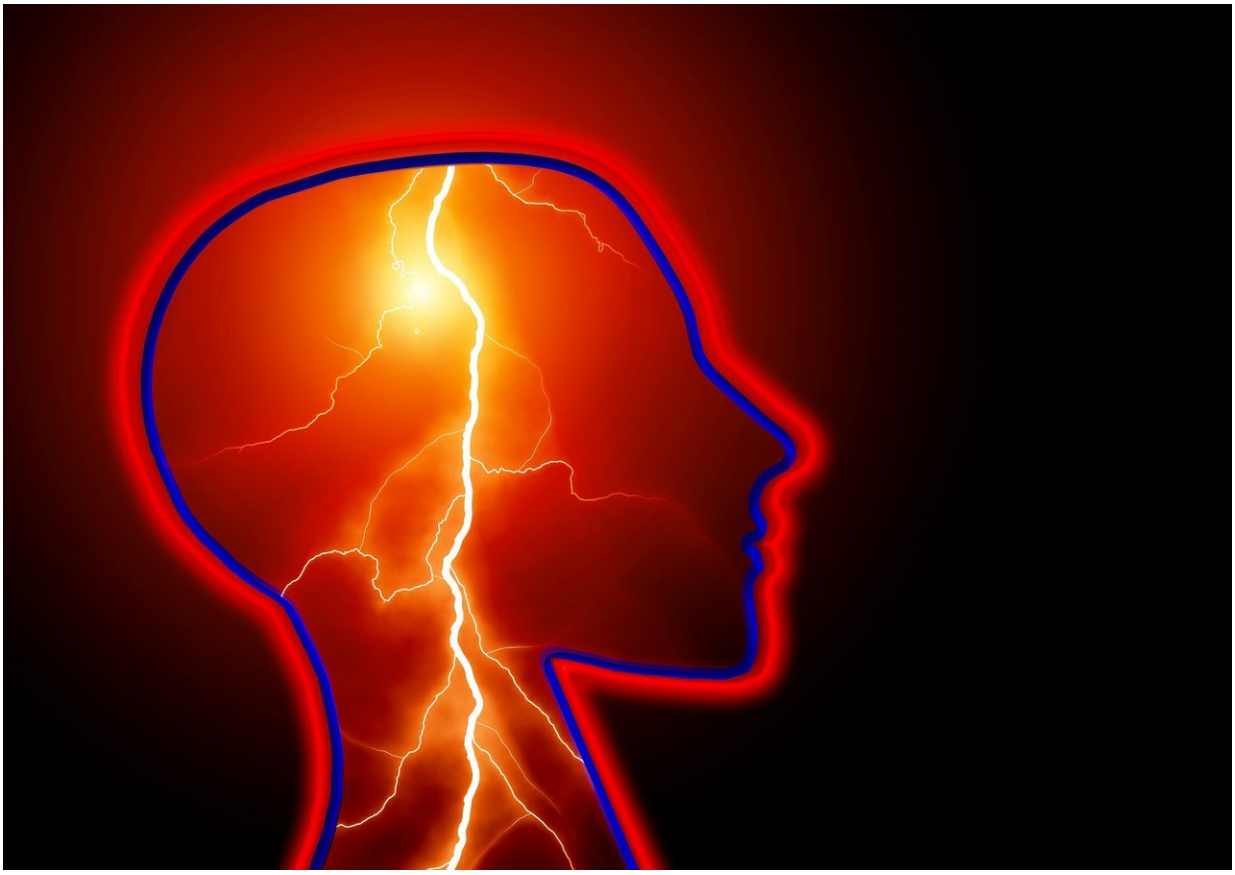

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Most seizure medications carry a life-and-death warning: Taking this drug may increase suicide risk. Now researchers, including Michael

Sperling, MD, a professor in the department of Neurology and Director of the Clinical Neurophysiology Laboratory and the Comprehensive Epilepsy Center at Thomas Jefferson University, have discovered that the warning does not apply to many antiseizure drugs.

A new analysis, initiated by Pavel Klein, MD, a neurologist at the Mid-Atlantic Epilepsy and Sleep Center in Bethesda revealed no evidence for increased suicide risk from recently developed antiseizure medications. Despite the lack of data, all anti-seizure medications carry the warning from the U.S. Food and Drug Administration (FDA). The findings, reported on August 2 in *JAMA Neurology,* call on the FDA to change its approach for applying class warnings to medication.

"The approach the FDA has taken is concerning for doctors and patients alike because it's not evidence based," says Dr. Sperling.

In 2008, the FDA analyzed results from nearly 200 clinical trials that assessed the efficacy of many drugs including 11 anti-seizure medications. The analysis revealed that compared with placebo, anti-seizure medications nearly doubled suicide risk among patients being treated for epilepsy, psychiatric disorders, and other diseases including chronic pain. The FDA concluded that anti-seizure medications increase suicide risk.

However, subsequent analyses did not find the same results. Yet, as a result of the FDA study, all anti-seizure medications approved since 2008 carry a warning for suicidality.

The warning affected the way new drugs are developed, which then impacted patient treatment. Trials of anti-seizure drugs since the warning came out have been careful to assess suicidality, but have also excluded people with histories of suicidal ideation. This means that trial results are difficult to extrapolate to patient treatment.

"Now when a patient with epilepsy and a history of suicidal ideation comes into my office, I know nothing about whether any drug that I could prescribe is particularly risky to that individual or not," Dr. Sperling said.

Another concern is that patients may be reluctant to start or keep taking anti-seizure medications because of the warning. For patients with epilepsy, however, not taking their medications could mean more seizures, and a risk of dying from increased seizures.

Drs. Klein and Sperling wanted to find out if the warning actually applied to drugs approved since the FDA's study in 2008.

The researchers reviewed all randomized, placebo-controlled phase II and III clinical trials of the five new antiseizures medications—eslicarbazepine, perampanel, brivaracetam, cannabidiol (epidiolex) and cenobamate—approved by the FDA since 2008 that assessed suicidality. In total, they evaluated the results of 17 studies involving nearly 6000 patients.

They found no evidence for increased risk of suicidal thinking or behavior in the five drugs. Suicidal thinking or behavior occurred in 12 of the 4000 actively-treated patients in the trial (0.3%) and seven out of nearly 2000 placebo-treated patients (0.35%).

"Our findings indicate the nonspecific suicide warning for all epilepsy drugs is simply not justifiable," says Dr. Sperling. "The results are not surprising. Different drugs affect cells in different ways. So there's no reason to expect that every drug would increase suicide risk for every patient."

Although he acknowledges that some patients with epilepsy have pre-existing depression and perhaps are at greater risk for suicidal ideation,

most do not.

"There's no reason to think that somebody with no history of depression and no risk for it would necessarily be at an increased risk for suicidality," he adds.

As some of the same brain chemistry that underlies epilepsy may be at play in depression, Dr. Sperling advises patients to pay attention to how they are feeling and to let their doctors know if they are having suicidal thoughts.

"Patients and doctors must balance risks. The risk of epilepsy and seizures that are not controlled is greater than the risk of suicidality from anti-seizure medications that the FDA has highlighted," he says.

Dr. Sperling hopes that the evidence speaks for itself and that the FDA will reconsider their blanket-warnings on classes of drugs. "Without the evidence to support it, the net effect of such class risk on drugs have consequences that may be worse if patients are afraid to take their medication," he says.

More information: Klein, P., Devinsky, O., French, J., Harden C., Krauss, G., McCarter, R., and Sperling. M. "Suicidality risk of newer anti-seizure medications: a meta-analysis," *JAMA Neurology* (2021). DOI: 10.1001/jamaneurol.2021.2480

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