Could antidepressants help reduce the risk of sudden unexpected death in epilepsy?

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A groundbreaking study published in Elsevier's *Epilepsy & Behavior* provides evidence in mouse model that drugs known as Selective Serotonin Reuptake Inhibitors (SSRIs; one category of antidepressants) may reduce the risk of Sudden Unexpected Death in Epilepsy (SUDEP).

SUDEP is estimated to be the cause of death in up to 17% of patients with epilepsy who die from their condition. Evidence for cardiac and respiratory causes of SUDEP has been presented, but no effective prevention of SUDEP has yet been developed.

Several studies have proposed that DBA mouse models of seizure-induced sudden death that are due to respiratory arrest may be useful models for respiratory-related causes of SUDEP. In these models, the generalized convulsive seizure is induced by acoustic stimuli, and the incidence of death after the seizure can be greatly reduced or prevented by providing rapid respiratory support.

A pharmacological approach to preventing respiratory failure in DBA/2 mice has also been developed, based on the well-established role of serotonin (5-hydroxytryptamine, 5-HT) in normal respiration. 5-HT is known to work on the brainstem respiratory network to enhance respiration in response to elevated levels of carbon dioxide. Carbon dioxide levels in patients with epilepsy are known to rise in association with generalized convulsive seizures, likely as a result of the accompanying respiratory depression as well as respiration difficulties during and after seizures, and have been well-described and speculated

to be associated with SUDEP in some cases.

The study presented in Epilepsy & Behavior, conducted by Dr. Faingold from Southern Illinois University School of Medicine and his colleagues, evaluated whether administration of an agent that enhances the availability of 5-HT, the SSRI fluoxetine, would be effective in preventing sudden death in DBA/1 mice.

The study found that semi-chronic (5-day) treatment with fluoxetine is a useful approach to prevent sudden death in the DBA/1 mice SUDEP model in doses that did not suppress the seizures. This effect was temporary, and susceptibility to sudden death returned 1-3 days after fluoxetine treatment. Future studies with other SSRIs and other selective 5-HT agonists, as well as longer-term treatment paradigms to evaluate these issues more thoroughly, will need to be performed.

"Dr. Faingold and colleagues have made a very important observation which, with further study, holds the promise for the development of treatments to lessen the risk of the devastating problem of SUDEP," added Steven C. Schachter, MD, Professor of Neurology at Harvard Medical School and Editor-in-Chief of Epilepsy & Behavior.

Dr. George Richerson, Chairman of Neurology at the University of Iowa and an expert on 5-HT, breathing and SUDEP said of the presented results, "This paper is a major advance, because it shows in a well-validated animal model that semi-chronic treatment with a safe and widely used drug can prevent both respiratory arrest and sudden death. Although this does not directly prove that this approach would be effective in humans, it provides a strong rationale for clinical trials to prevent the most common cause of death in epilepsy patients, which has previously been unpreventable."

Elson L. So, MD, Second Vice-President of the American Epilepsy

Society and Professor of Neurology at Mayo Clinic College of Medicine said, "The findings in this study are very important because they reveal very specific mechanisms that could explain the impaired breathing that is known to occur with seizures in many persons with epilepsy. Moreover, studies along this line may eventually lead to the use of currently available medicines in persons with poorly controlled seizures to reduce their risk for SUDEP."

"This is a significant development in SUDEP research. Not one more life should be lost to epilepsy; it's studies like this that will make that dream a reality," Jeanne Donalty member of the CURE Board of Directors stated. Dr. Faingold's research was sponsored by CURE.

More information: The article is "Prevention of seizure-induced sudden death in a chronic SUDEP model by semichronic administration of a selective serotonin reuptake inhibitor" by Carl L. Faingold, Srinivasan Tupal, and Marcus Randall (doi:10.1016/j.yebeh.2011.06.015). The article appears in Epilepsy & Behavior, Volume 22, Issue 2 (October, 2011)

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