

Alzheimer's Drug Linked to Potentially Serious Muscle Condition

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The Alzheimer's drug donepezil (multiple brands) is associated with a twofold higher risk for hospital admission for rhabdomyolysis, a rare but potentially life-threatening condition in which muscle cells break down. It can lead to kidney damage.

Results of a population-based study showed that use of donepezil was associated a significantly higher risk for rhabdomyolysis compared to other cholinesterase inhibitors, although the investigators note that the absolute risk was small.

"Clinicians should have an index of suspicion to check for rhabdomyolysis if patients on donepezil present with muscle weakness or pain," study investigator Jamie Fleet, MD, Department of Physical Medicine and Rehabilitation at McMaster University, Hamilton, Ontario, Canada, told *Medscape Medical News*.

"There was some concern about the risk of rhabdomyolysis in donepezil use based on case reports. It was flagged by Health Canada and other regulatory agencies as a potential risk, which was one of the main reasons behind our study," Fleet added.

The study was [published online](#) September 16 in *CMAJ (Canadian Medical Association Journal)*.

Support for Regulatory Warnings

The researchers analyzed data from 2002 to 2017 on 220,353 patients aged 66 years or older who had received a new prescription for one of three cholinesterase inhibitors that are used to manage AD and other dementias. Those three drugs are donepezil, rivastigmine (*Exelon*, Novartis), and galantamine (*Razadyne*, Janssen).

For patients who received donepezil, there was a higher risk for hospitalization for rhabdomyolysis compared with their peers who took either rivastigmine or galantamine (88 events in 152,300 patients [0.06%] vs 16 events in 68,053 patients [0.02%]). The weighted odds ratio with donepezil was 2.21 (95% confidence interval, 1.52 – 3.22). Baseline use of a statin did not alter the results.

"The findings of this population-based cohort study support regulatory agency warnings about the risk of donepezil-induced rhabdomyolysis," the researchers write. "Reassuringly, the 30-day incidence of a hospital admission with rhabdomyolysis after initiating donepezil remains low," they add.

Fleet said it is important to note that most cases of rhabdomyolysis that occurred after use of donepezil were not severe and that none of the patients had to undergo acute dialysis or mechanical ventilation.

As for the biological mechanism of donepezil-associated rhabdomyolysis, acetylcholine plays a role in the transmission of action potential across the neuromuscular junction, leading to muscle contraction. Theoretically, prevention of the breakdown of acetylcholine may lead to abnormalities in muscle contraction and ultimately rhabdomyolysis, but this "warrants further research," the authors note.

Donepezil the Only Culprit?

Reached for comment, Gregory Jicha, MD, PhD, of the Sanders-Brown Center on Aging, University of Kentucky, Lexington, noted that a "small subset of patients can experience muscle cramping as one of the side effects of cholinesterase inhibitors.

"This is something that has been watched for some time. This very large study certainly puts it on our radar; but that said, this is an incredibly rare side effect, and in the majority of the patients, the symptoms were quite mild," Jicha told *Medscape Medical News*.

"Unless there is something in the patient's history to suggest they may be predisposed to rhabdomyolysis, it has not been a common part of clinical discussions. Certainly if you have a patient on one of these medicines and they come into the emergency department with unexplained rhabdomyolysis, one should be aware that that this is one potential cause."

In addition, Jicha said he does not believe donepezil should be singled out.

"From a scientific plausibility standpoint, it doesn't make sense that one cholinesterase inhibitor would be worse than another. It could be that the groups in this study were imbalanced," he said.

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