MedicalXpress

Statins linked to lower aggression in men, but higher in women

July 1 2015

Statins are a hugely popular drug class used to manage blood cholesterol levels and reduce the risk of heart disease. Previous studies had raised questions about adverse behavioral changes with statins, such as irritability or violence, but findings with statins have been inconsistent. In the first randomized trial to look at statin effects on behavior, researchers at the University of California, San Diego School of Medicine report that aggressive behavior typically declined among men placed on statins (compared to placebo), but typically increased among women placed on statins.

The findings are published July 1 in the online issue of *PLOS ONE*.

"Many studies have linked low cholesterol to increased risk of violent actions and death from violence, defined as death from suicide, accident and homicide," said lead author Beatrice A. Golomb, M.D., Ph.D., professor of medicine. "There have been reports of some individuals reproducibly developing irritability or aggression when placed on statins. Yet in contrast to pre-statin lipid-lowering approaches, clinical trials and meta-analyses of statin use (in which most study participants were male) had not shown an overall tendency toward increased violent death. We wanted to better understand whether and how statins might affect aggression."

Researchers randomly assigned more than 1,000 adult men and postmenopausal women to either a statin (simvastatin or pravastatin) or a placebo for six months. Neither researchers nor trial participants knew

who was receiving the drug or the placebo. Behavioral aggression was measured using a weighted tally of actual aggressive acts against others, self or objects in the prior week.

Other measurements taken included testosterone levels and reported sleep problems. Simvastatin is known to affect both measures, said Golomb, and both testosterone and sleep can affect aggression.

The male and female study cohorts were separately randomized, and analyzed separately since it was shown that statin use affected the genders differently.

For postmenopausal women, said the scientists, the typical effect was increased aggression. The effect was significant for postmenopausal women older than age 45. The increase in aggression (compared to placebo) appeared stronger in women who began with lower aggression at baseline.

For men, the picture was more complex. Three male participants who took statins (and no one on placebo) displayed very large increases in aggression. When these were included in analysis, there was no average effect. When these "outliers" were removed from the analysis, a decline in aggressive behavior for male statin users was significant. It was stronger among younger men who tend to be more aggressive. "But actually the effect was most evident in less aggressive men," said Golomb.

Examination revealed statin effects on testosterone and sleep contributed to bidirectional effects. "Changes in testosterone and in sleep problems on simvastatin each significantly predicted changes in aggression. A larger drop in testosterone on simvastatin was linked, on average, to a greater drop in aggression. A greater rise in sleep problems on simvastatin was significantly linked to a greater rise in aggression. The

sleep finding also helped account for the outliers: The two men with the biggest aggression increases were both on simvastatin, and both had developed 'much worse' sleep problems on the statin."

The full set of biological explanations linking statins to behavior remains a work-in-progress. One early hypothesis was that lower levels of cholesterol may reduce brain serotonin. (The connection between low brain serotonin activity and violence has been viewed as one of the most consistent findings in biological psychiatry.) Whole blood serotonin—which can relate inversely to brain serotonin—was not a predictor in this study. However, testosterone and sleep were, for those on simvastatin. Golomb postulates that other factors, such as oxidative stress and cell energy, may play a role. She noted that the findings help clarify seeming inconsistencies in the scientific literature.

"The data reprise the finding that statins don't affect all people equally—effects differ in men versus women and younger versus older. Female sex and older age have predicted less favorable effects of statins on a number of other outcomes as well, including survival."

Bottom line, said Golomb: "Either men or women can experience increased aggression on statins, but in men the typical effect is reduction."

Provided by University of California - San Diego