Antipsychotic drugs linked to increased mortality among Parkinson's disease patients

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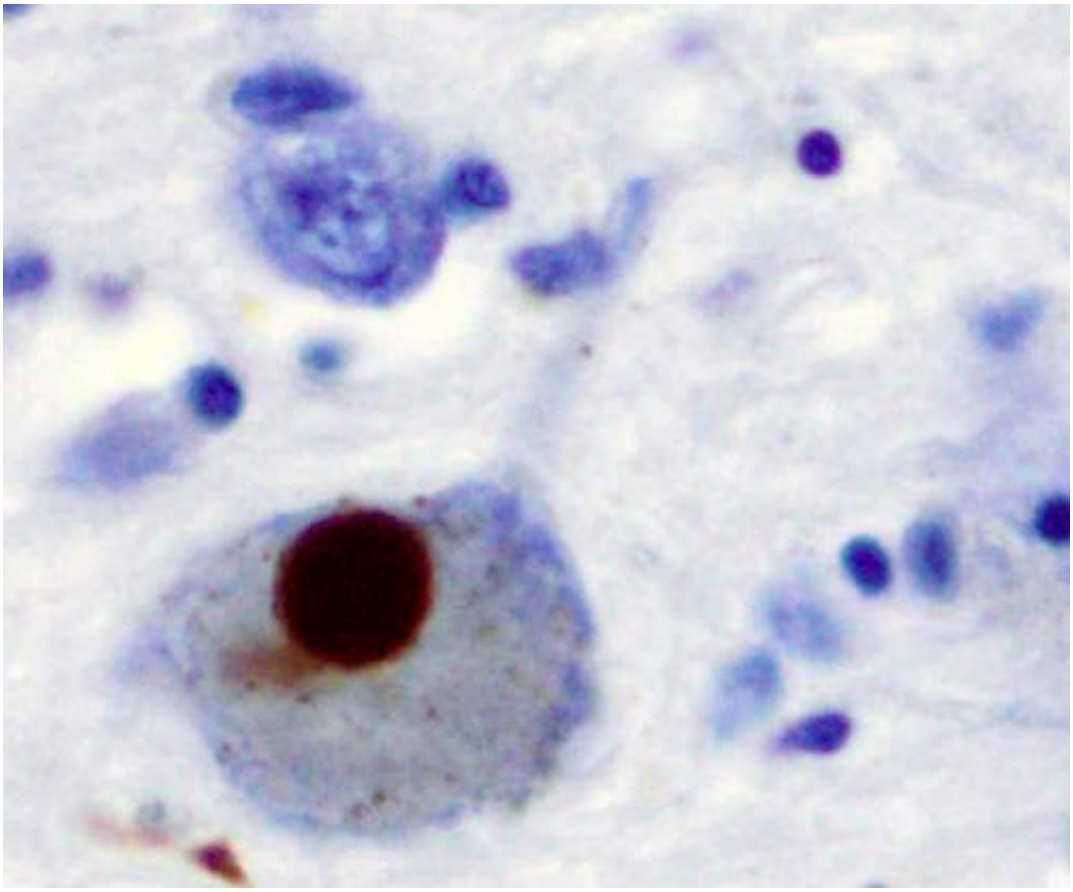

Immunohistochemistry for alpha-synuclein showing positive staining (brown) of an intraneural Lewy-body in the Substantia nigra in Parkinson's disease. Credit: Wikipedia

At least half of Parkinson's disease patients experience psychosis at

some point during the course of their illness, and physicians commonly prescribe antipsychotic drugs, such as quetiapine, to treat the condition. However, a new study by researchers at the Perelman School of Medicine at the University of Pennsylvania, the University of Michigan Medical School, and the Philadelphia and Ann Arbor Veterans Affairs (VA) Medical Centers and suggests that these drugs may do significantly more harm in a subset of patients. The findings will be published in the March 21, 2016 issue of *JAMA Neurology*.

The researchers' analysis of about 15,000 patient records in a VA database found that Parkinson's patients who began using antipsychotic drugs were more than twice as likely to die during the following six months, compared to a matched set of Parkinson's patients who did not use such drugs.

"I think that antipsychotic drugs should not be prescribed to Parkinson's patients without careful consideration," said senior author Daniel Weintraub, MD, who is an associate professor of Psychiatry and Neurology at Penn Medicine and a fellow in Penn's Institute on Aging.

These findings are not the first to link antipsychotic drugs to increased mortality. Studies dating back to the early 2000s have found increased mortality with antipsychotic use among patients who have dementia in the general population. Since 2005 the FDA has mandated "black box" warnings on antipsychotic drug packaging, noting the apparently increased risk of death when these drugs are used in dementia patients.

Although most dementia cases are accounted for by Alzheimer's disease, there are other forms of dementia, including one that eventually emerges in about 80 percent of Parkinson's patients, usually many years after their Parkinson's diagnosis. However, a study by Weintraub and colleagues in 2011 found that the FDA warnings had done little to curb antipsychotic prescriptions for Parkinson's dementia patients.

For the new study, Weintraub and his collaborators examined the possibility that antipsychotic drug use is associated with higher mortality not just in Parkinson's dementia patients, but in all Parkinson's disease patients. Psychosis in Parkinson's, although it is associated with dementia and later-stage disease, can occur even in the early stages of illness and in the absence of dementia. "It happens not uncommonly earlier in the course of the illness," Weintraub said.

The underlying causes of psychosis in Parkinson's are not well understood, but are thought to include the spread of the neurodegenerative disease process to certain brain areas, as well as particular or higher doses of Parkinson's drugs that enhance dopamine function.

For the study, the researchers examined records from a large Veterans Affairs database, comparing a group of 7,877 Parkinson's patients who were prescribed antipsychotic drugs at any time during 1999-2010 to an equal-sized "control group" of Parkinson's patients who did not use antipsychotic drugs. To reduce differences between the groups that could bias the comparison, the investigators paired each patient in the antipsychotic group with a control patient who was matched for age, gender, race, years since diagnosis, presence of dementia, and other relevant factors.

The analysis revealed that in the 180 days after they first took antipsychotic drugs, patients in the first group died in much larger numbers, compared with the matched control patients during the same periods. Overall the Parkinson's patients who used antipsychotics had 2.35 times the mortality of the non-users.

The relative risk seemed to vary by the specific drug—for example, 2.16 times higher for quetiapine fumarate compared with non-treatment, 2.46 for risperidone, 2.79 for olanzapine, and 5.08 for haloperidol. First-

generation or "typical" antipsychotics, which include haloperidol, collectively were associated with about 50 percent greater relative mortality risk, compared to more recently developed "atypical" antipsychotics such as risperidone and quetiapine.

Antipsychotic drugs have a variety of potential side-effects, including reduced alertness, increased risks of diabetes and heart disease, decreased blood pressure, and—with longer-term use—movement disorders that can resemble those seen in Parkinson's. The initial FDA warnings were based on findings of increased strokes among antipsychotic users. But researchers still do not fully understand why these drugs are linked to higher mortality in certain patient groups. "In this study we looked at the dataset for clues," said Weintraub, "but the most common cause of death listed was 'Parkinson's disease'—so there really wasn't anything that pointed to a specific cause or mechanism."

He and his colleagues are now conducting a follow-up study that might shed more light on that mechanism. They will examine the same VA database, looking not at mortality but at "morbidity"—disease diagnoses, injuries and other new episodes of ill-health—among Parkinson's patients taking antipsychotic drugs, comparing them with the same matched controls.

For the present, Weintraub suggests that neurologists and other physicians should prescribe antipsychotics to Parkinson's patients only after looking for other possible solutions, such as treating any co-morbid medical conditions associated with psychosis, reducing the dosage of dopamine replacement therapies, and simply managing the psychosis without antipsychotics.

"Antipsychotics should be used in these patients only when the psychosis is of clinical significance, and patients probably should not be left on these drugs long-term without re-evaluation," Weintraub said.