Antipsychotics Linked to Mortality in Parkinson's

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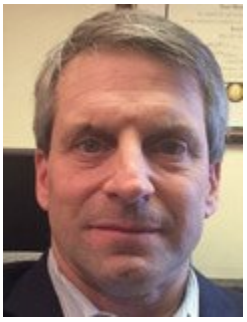
New research links antipsychotic use to increased mortality in patients with Parkinson's disease (PD).

A new analysis showed that patients with PD receiving an antipsychotic had more than twice the risk for death than patients with PD not taking one of these drugs.

Psychosis occurs in up to 60% of patients with PD, many of whom receive an antipsychotic, lead author, Daniel Weintraub, MD, associate professor, Psychiatry, University of Pennsylvania, Philadelphia, told *Medscape Medical News*. But because little evidence supports the use of these drugs in PD, they should be prescribed cautiously in this population.

"Now that we have this additional data that suggests that their use may also be associated with an increased risk of mortality, they should be used even more cautiously."



Dr Daniel Weintraub

The study, a collaborative research project among Dr Weintraub, senior author Helen Kates, MD, professor, psychiatry, University of Michigan, Ann Arbor, and colleagues, was published online March 21 in *JAMA Neurology*.

He presented some of these findings in 2015 at the International Parkinson and Movement Disorder Society (MDS) 19th International Congress, reported by *Medscape Medical News* at that time.

In addition to the 60% of patients with PD who experience psychosis, 80% develop dementia, and the use of antipsychotics in the population with PD is common, the authors write.

In 2005, the US Food and Drug Administration (FDA) issued an advisory that warned treating behavioral disorders in elderly patients with dementia in the general population by using atypical antipsychotics is associated with increased mortality. A similar FDA alert was issued in 2008 for

typical antipsychotics. However, whether this risk extends to patients with dementia associated with PD "remains unknown," they note.

Dr Weintraub and his research team used national Veterans Affairs health system administrative data to examine 180-day mortality risks for patients with PD from 1999 to 2010.

They compared 7877 mostly male patients, mean age about 76 years, who filled a new antipsychotic prescription, to a matched group of patients with PD who didn't use antipsychotics.

Atypical and Typical

Of the antipsychotic prescriptions, 5.5% were for typical (or conventional) agents, with haloperidol being the most commonly prescribed. The most commonly prescribed atypical antipsychotic agent was quetiapine (66.9%), followed by risperidone and olanzapine.

"Clinicians are comfortable with quetiapine and feel it can be effective and well tolerated," commented Dr Weintraub.

Typical antipsychotics are usually older agents that focus on the dopaminergic system in terms of receptor blockage, whereas the newer atypicals tend to affect the serotonergic as well as the dopaminergic system, he said.

After adjustment for covariates, patients taking antipsychotics had more than a 2-fold higher risk for death compared with patients not prescribed these drugs (hazard ratio [HR], in the intention-to-treat [ITT] analysis, 2.35; 95% confidence interval [CI], 2.08 - 2.66; $P < .001$).

An ITT analysis by antipsychotic type showed higher risks for both atypical (HR, 2.26; 95% CI, 1.98 - 2.57) and typical (HR, 3.65; 95% CI, 2.47 - 5.39) medications ($P < .001$ for both).

Quetiapine had a "relatively good" mortality risk compared with other agents, although it was still elevated, said Dr Weintraub.

Using quetiapine, the most commonly prescribed antipsychotic in PD, as a reference, the researchers found increased mortality risks for, in descending order in the ITT analysis, haloperidol (HR, 1.85), other typical antipsychotics (HR, 1.54), olanzapine (HR, 1.47), and risperidone (HR, 1.30).

To account for the possibility that palliative care patients might be prescribed antipsychotics, the researchers excluded patients who died within 4 weeks of the index date. That analysis found similar mortality HRs.

The leading cause of death among patients exposed to antipsychotics was PD. It was listed as the cause in 53.2% of these deaths, which was 38% higher than for deaths among patients not exposed to antipsychotics. Other causes of death that were more common among antipsychotic users included influenza and pneumonia.

Adverse effects of antipsychotics can include increased sedation, falls, and difficulty swallowing, said Dr. Weintraub. He added that patients with PD already have balance, gait, and swallowing problems.

Although the researchers made every effort to match the two study groups, there was no direct measure of PD severity. It's possible, said Dr Weintraub, that those who used antipsychotics had worse PD to begin with.

So the increased mortality among antipsychotic users could be because patients with PD taking these drugs are more disabled than those who don't take them, or the medications themselves increase the risk for death. "Or it could be a mix of the two," said Dr Weintraub.

Because the cohort was mostly men, would the results be the same in women? "None of us is aware of any data suggesting differential mortality rates for men and women with antipsychotic use," noted Dr Weintraub.

He added that two thirds of patients with PD are men, so most patients with PD receiving an antipsychotic would be men.

In patients with PD, antipsychotics should be used only after very careful consideration, ruling out comorbid medical conditions, such as an infection, and adjusting PD medications, said Dr Weintraub.

Clinicians might also consider behavioral strategies to try to manage psychotic symptoms, he added.

"If all else fails, and the patient is still having clinically meaningful symptoms, then it may be that an antipsychotic trial is needed," said Dr Weintraub. He stressed that if this is the case, the patient and family should be informed of a possible increased risk for death.

Although quetiapine is the most commonly used agent to treat psychosis in PD, no randomized controlled trials (RCTs) support this use, said Dr Weintraub. The only medication that has been shown in RCTs to be efficacious for PD psychosis is clozapine, but it's rarely used because it requires regular blood tests to monitor for agranulocytosis, an acute condition involving severe leukopenia.

Clinicians could try using a lower dose of an antipsychotic because higher doses may be more likely to cause adverse effects. They may also consider treating patients for a limited period.

"It's possible that someone could be treated for X period of weeks or months and then re-evaluated about the need for ongoing treatment," said Dr Weintraub.

A drug developed specifically for PD psychosis, pimavanserin (*Nuplazid*, Acadia Pharmaceuticals) is being considered today by the FDA's Psychopharmacologic Drugs Advisory Committee.

Major Implications

In light of the "major implications" of this new study, its limitations should be "thoroughly" considered, says Mark Baron, MD, Department of Neurology, Virginia Commonwealth University Health System, Richmond, in an accompanying editorial.

One limitation is that the PD diagnosis was not restricted to specialists and the study didn't provide sources for the diagnoses. Autopsy studies, notes Dr Baron, show a relatively high diagnostic inaccuracy for PD, even among movement disorder specialists.

Also, he says, it's uncertain whether the underlying psychosis or the treatment itself poses the risk for mortality.

Dr Baron notes that in the study PD was listed as the number 1 cause of death in the treated group and was second to cardiovascular disease in the untreated group.

"As acknowledged by the authors, this finding could support a contribution of worsening parkinsonism with many of these agents owing to dopamine blockade. The extent to which worsening parkinsonism might contribute to the observed greater associated mortality with the use of conventional vs second-generation APs has not been addressed adequately," he writes.

"Faced with a patient with PD who has uncontrollable hallucinations," he continues, "health care professionals are confronted with a difficult situation, often with no effective and clearly safe approaches."

In addition to "removing any potential offending agents, especially any antiparkinsonians besides levodopa" and if unsuccessful, cautiously lowering the levodopa dose with a plan to quickly increase it if the desired effect isn't achieved, Dr Baron suggests trying such agents as cholinesterase inhibitors.

If an antipsychotic is used, "atypical agents with the least potential risk for mortality and the lowest associated risk for worsening parkinsonism should be prescribed," he says. "The therapy should be started at low doses and titrated slowly to the lowest effective dose."

However, many families, when learning of the boxed warning, are resistant to considering introducing an antipsychotic, he says.

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