

NEWS

Flawed protocol for levodopa clinical trial brings retractions

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Two studies conducted at the New York State Psychiatric Institute in New York City have been withdrawn because the researchers violated their own study protocol.

The studies were based on a clinical trial that began in 2016 and tested whether treatment with the Parkinson's disease drug levodopa could improve mood and mobility in older adults with depression. **Bret Rutherford**, a psychiatrist at Columbia University, led the research. Participants were **able to walk faster** after taking levodopa and experienced a **reduction in their depressive symptoms**, the studies found, suggesting the strategy had promise.

But those articles have since been withdrawn. A brief **retraction notice** for one of the studies was published in the June 2023 issue of the *Journal of Affective Disorders*. It noted that the paper (originally published in March 2020) had been removed at the request of the authors, who no longer had “full confidence in the article's conclusions” because of “errors and omissions” in their description of the study participants and their response to levodopa.

“Correcting the errors affected the manuscript sufficiently that we thought it would be better to retract the initial manuscript and to replace it with a new version that could put the changes in context.” John Krystal

Biological Psychiatry published a more detailed **retraction notice** for the other study in February 2023, indicating that the article (originally published in April 2019) had been retracted at the request

of the editor because of “irregularities and deviations from the approved protocol.”

That editor, **John Krystal**, professor of psychiatry at the Yale School of Medicine, says the mistakes were “straightforward errors” and that he doesn’t believe there was anything “particularly concerning” about his interactions with Rutherford. “Correcting the errors affected the manuscript sufficiently that we thought it would be better to retract the initial manuscript and to replace it with a new version that could put the changes in context,” he says.

The problems stem from the study population. Participants were supposed to have been excluded if they had received any antidepressant medications in the past 28 days. (Some antidepressant medications, including Prozac and other selective serotonin uptake inhibitors, are known to **influence dopamine levels in the brain**.) But 8 of 36 participants had not completed the required washout period, and at least one had taken antidepressant medication the day before the study began. The notice also indicated that three participants had been included in the study even though their low score on a depression survey should have excluded them.

In addition to the retractions, two of Rutherford’s articles based on a **related clinical trial** that began in 2014 have also been corrected. The **corrections**, both **published** in the *American Journal of Geriatric Psychiatry* in January, point to similar problems with the study protocol, though the authors say the deviations do not alter the validity of the results. “It was always our intention, as described in the original grant application, to offer study participation to individuals taking an ineffective antidepressant medication so long as they underwent a study-supervised medication taper,” the authors write in one of the notices.

It is not clear how the screening errors were made or how they came to light. Rutherford did not respond to multiple requests for comment, nor did the lead investigator on all four papers, **Steven Roose**, professor of clinical psychiatry at Columbia University.

The National Institute of Mental Health (NIMH), which **has been funding** Rutherford’s levodopa research since 2016, **stopped** one of his trials last year, and a separate trial is listed as **temporarily suspended**, according to ClinicalTrials.gov.

Rutherford also received a K24 Midcareer Award from the NIMH in 2020 based on his levodopa work. These awards are granted for up to five years and can be renewed for an additional three to five years. Rutherford, however, was funded **for just a single year**.

Carla Cantor, director of communications at the New York State Psychiatric Institute, declined to comment, and the NIMH declined to provide any additional information regarding the suspension of the trials.

The development was a disappointment to **Steven Dubovsky**, professor and chair of the psychiatry department at the University at Buffalo in New York, who had highlighted the findings in

a column in the *New England Journal of Medicine* in 2019. Dubovsky had noted then that, although the results were preliminary, “clinicians might consider levodopa for patients whose psychomotor function or cognition does not improve with treatment of depression.”

Following the retractions, Dubovsky says that the methodological errors were “trivial” and that he hopes a larger and more robust clinical trial will be conducted in the future.

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