sion.[2-4] Both DBS and LCIG are treatment options in patients having a similar degree of motor impairment. Though it is well recognized that STN DBS may increase the risk of suicide, possibly through increased impulsiveness,[2] the data for LCIG are still emerging, with only 3 cases of suicide reported thus far.[1,5] Our first patient, although clinically not noted to be depressed, experienced recent discontinuation of DA, which could have resulted in DA withdrawal syndrome, known to be associated with depression and suicide.[2] Our second patient had multiple risk factors associated with suicide, including depression and PD-related psychosis. Motor improvement achieved by LCIG could have been coupled with different triggering factors in our patients, resulting in suicide. The suicide percentage of 0.5% per year in our LCIG-treated patients is well above the suicide rate in Slovenia for the age-matched population (33 in 100,000 per year). Evidence of LCIG being directly or indirectly associated with suicidal behavior remains meager, but careful documentation of possible suicidal ideation and circumstances is important given that it may help in identification of potential risk factors. ■

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References

1. Fernandez HH, Standaert DG, Hauser RA, et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month, open-label results. Mov Disord 2015;30:500-509.
2. Voon V, Krack P, Lang AE, et al. A multicentre study on suicide outcomes following subthalamic stimulation for Parkinson's disease. Brain 2008;131:2720-2728.
3. Myslobodsky M, Lalonde FM, Hicks L. Are patients with Parkinson's disease suicidal? J Geriatr Psychiatry Neurol 2001;14:120-124.
4. Kostić VS, Pekmezović T, Tomić A, et al. Suicide and suicidal ideation in Parkinson's disease. J Neurol Sci 2010;15;289:40-43.
5. Santos-Garcia D, Macias M, Llaneza M, Aneiros A. Suicide following duodenal levodopa infusion for Parkinson's disease. Mov Disord 2009;24:2029-2030.

Reply to Letter: Suicide in Parkinson's Disease Patients Treated With Levodopa-Carbidopa Intestinal Gel

We thank Dr. Zorko and colleagues for their interest in our article and for bringing greater attention to this issue. We agree that susceptibility to suicide and suicidal ideation is a very serious issue in patients with Parkinson's disease (PD).

Our 12-month clinical study monitored safety in 354 enrolled patients at 86 centers in 16 countries, 272 of whom completed the study. Whereas the 12-month outcomes of this study described in our article included 2 cases of suicide (2 of 354; 0.6%), it is important to note that long-term follow-up of this cohort and all others in the LCIG U.S. registration program continues (n = 416, with >950 total patient-years of follow-up). To date, no additional cases of suicide have been reported. Both of the cases of suicide described in our report were considered "unrelated to the treatment" based on the opinion of the local study investigators responsible for the care of these patients. In agreement with the risk factors noted in the cases described by Zorko et al., both patients in the study had relevant medical histories of depression.

Although historically suicide rates were thought to be low in the PD population, more-recent studies report a broad range of rates of suicidal ideation (0.9%–11%) and completed suicides (0.8% up to 7%).[1-4] None of these studies, however, address the important question of whether this suicidality relates to the disease itself or a specific medical treatment. As a cautionary example, there were a few alarming case reports and observational studies suggesting that DBS led to a higher incidence of suicide in PD patients; however, these were refuted by a larger, prospective, randomized, controlled trial showing no association between DBS and suicidal ideation or behaviors.[2]

There is much that is still unknown about the relationship between suicide, age, medical treatment, and disease in the PD patient population. Depression is a common comorbidity in PD patients, and in a multivariate analysis, severity of depression was the only predictor of suicide or death ideation for PD patients.[1] Furthermore, depression has been associated with levodopa use and is described as an adverse event (with or without development of suicidal tendencies) in the U.S. Food and Drug Administration label for oral carbidopa/L-dopa.[5] Until more scientifically robust data are available, we believe that the best approach is continued vigilance in all patients for signs of depression and suicidality. At this time,

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the evidence for any causal relationship between suicide, PD, and treatments for PD is inconclusive. ■

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References

1. Nazem S, Siderowf AD, Duda JE, et al. Suicidal and death ideation in Parkinson's disease. Mov Disord 2008;10:1573-1579.
2. Weintraub D, Duda JE, Carlson K, et al. J Neurol Neurosurg Psychiatry 2013;84:1113-1118.
3. Schuepbach WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med 2013;368:610-622.
4. Di Rocco A, Molinari SP, Kollmeier B, et al. Parkinson's disease: progression and mortality in the L-DOPA era. Adv Neurol 1996; 69:3-11.
5. Sinemet [package insert]. Whitehouse Station, NJ; Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.; 2011.

Hyposmia in SWEDD

We read with great interest the article by Sprenger and colleagues[1] in which they report non-motor symptoms in subjects with suspected parkinsonism and scans without evidence of dopaminergic deficit (SWEDD). They analyze the data from 412 patients with PD, 184 healthy controls, and 62 patients with SWEDD included in the Parkinson's Progression Marker Initiative study on various non-motor symptom (NMS) questionnaires. Results show that overall NMS were more common in patients with SWEDD than in healthy controls, including hyposmia: 12 of 62 (19.4%) of patients with SWEDD were hyposmic compared with 12 of 184 (6.5%) of controls (P = 0.003). Of 412 PD subjects, 276 (67%) were considered hyposmic using the same cutoff value.

We had previously reported[2] that in 21 patients with SWEDD recruited from Queen Square (London, UK) and Glasgow (UK), the average score on the 40-item University of Pennsylvania Smell Identification Test (UPSIT) was 27.3 (standard deviation [SD] = 5.0), which was significantly higher than in 191 patients with PD (average, 17.6; SD, 6.2), rendering smell tests useful in the differentiation between PD and SWEDD. The small difference between the average score in patients with SWEDD and healthy controls (average, 29.5; SD, 5.3) was not significant in the multivariate analyses performed in our study (P = 0.7).

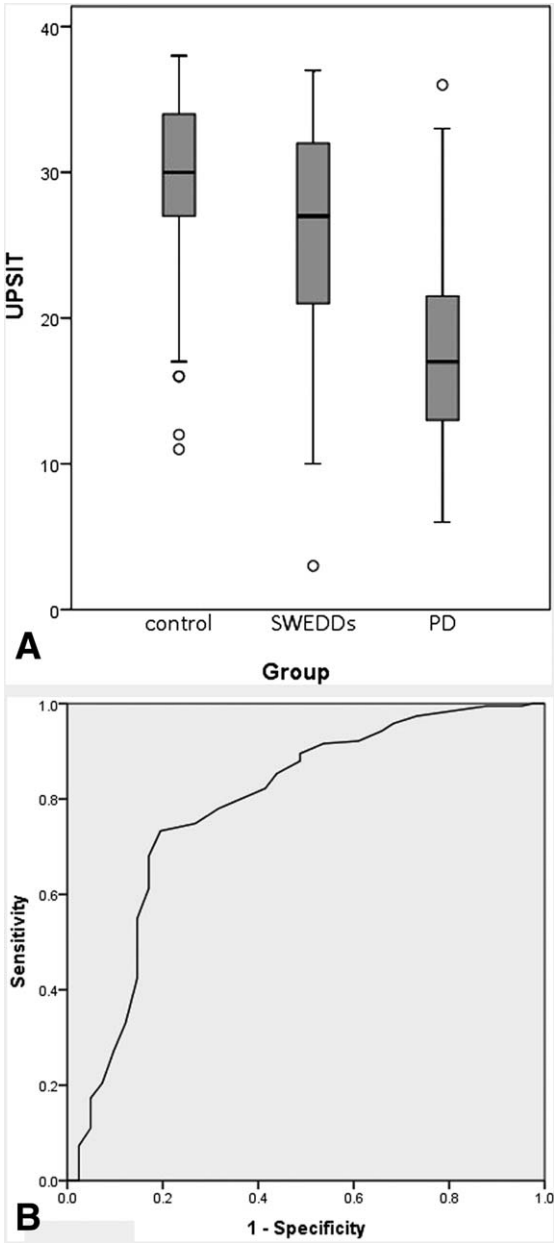

FIG. 1. Olfaction in suspected parkinsonism without evidence of dopaminergic deficit (SWEDD) compared with Parkinson's disease and control.(**A**) Box plot showing the median (the horizontal line) within a box containing the central 50% of the observations (ie, the upper and lower limits of the box are the 75th and 25th percentiles) and extremes of the "whiskers" containing the central 95% of the ordered observations for each group of subjects. Outliers are showed as circles. (**B**) Receiver operating characteristic curve for the use of UPSIT differentiating PD (status = 1) from SWEDD (status = 0). PD, Parkinson's disease; SWEDD, subjects with suspected parkinsonism without evidence of dopaminergic deficit; UPSIT, 40-item University of Pennsylvania Smell Identification Test.

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