Suicide Risk in Parkinson's Disease

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Patient Vignette

A 48-year-old man was evaluated in a movement disorders center for consideration of deep brain stimulation for advanced Parkinson's disease (PD). He developed symptoms of PD at the age of 39 and had received treatment with levodopa and dopamine agonists for 8 years. His current problems included marked motor fluctuations requiring him to take levodopa every 2 hours and moderately severe peak-dose dyskinesias. Neuropsychological testing revealed no cognitive impairment. As part of his preoperative evaluation, psychiatric evaluation revealed an underlying mild to moderate depression and mild anxiety. Social support was limited, as he lived alone with one sibling located in the area. He was currently retired on medical disability.

He underwent successful implantation of bilateral subthalamic deep brain stimulators without incident. Postoperative course was uneventful, and there was substantial improvement in his motor performance, with reduction in his levodopa by 60%. Despite this improvement, his depression worsened postoperatively, and close evaluation by his psychiatrist revealed mild suicidal ideation, with some thoughts of a plan. He was admitted to the psychiatry service, and a course of antidepressants was begun. Psychotherapy and supportive counselling were also engaged. His depression improved, and he was ultimately discharged home. One year later, his depression remains well controlled.

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Introduction

Parkinson's disease (PD) is characterized by a range of disease- or medication-related neuropsychiatric symptoms including depression, apathy, psychosis, anxiety, and cognitive and behavioral changes. Recent studies suggest the rates of completed suicides in PD to be greater than the general population [1]. Suicidal ideation appears to be common in PD. Suicide is a major but possibly preventable public health issue identified by the World Health Organization as one of the top ten causes of death. Suicide is multifactorial and is associated in the general population with depression, gender, age, marital status, comorbid physical illness, and previous suicide attempts [2]. In this chapter, the studies on suicidal behaviors in PD are reviewed and categorized into suicidal ideation and completed suicides.

Suicidal Ideation

Suicidal ideation is common in PD, reported across multiple studies between 12% and 30% of PD patients [3–7]. Suicidal ideation is most commonly associated with depression, reported in almost all studies. Other mental health symptoms such as psychosis, anxiety, impulse control disorders, and hopelessness have also been reported to be elevated [4]. Demographic factors such as lower age and PD-related factors such as lower age of PD onset, greater motor complications, more non-motor symptoms, and greater perceived disability are also associated with suicidal ideation [4, 5]. Suicidal ideation was increased in early-onset PD ($N = 577$) relative to late-onset PD ($N = 2973$) (22% vs. 13%) with ideation associated with depression, dyskinesias, nonsmoking, lower education, and higher non-motor symptoms [8].

Completed Suicides

An early study suggested completed suicides may be lower than the general population although multiple more recent studies have challenged this observation. Using the US National Centre of Health Statistics mortality database from 144,364 patients with PD, 122 (0.08%) had committed suicide, a rate 10 times lower than that of the general population (0.8%) [9]. The PD patients with completed suicides had higher rates of depression compared to PD patients who died from other causes, again emphasizing the role of depression. In a smaller study using the Ontario provincial coroner's records with prescription records as a marker of illness from 1354 elderly patients who had died by suicide, suicide was not more or less likely to occur with PD (odds ratio on multivariate analysis: 1.11) as compared to other medical disorders such as congestive heart failure, chronic lung disease, and seizures (odds ratio: 1.30–2.41) and psychiatric disorders (odds ratio: 2.60–3.94) [10]. Similarly, in a

large Finnish database study of 555 hospital-treated patients above the age of 50 who had completed suicide, only 1.6% of all subjects were PD patients [11]. Previous suicide attempts in PD patients were common, occurring in 44% of cases as compared to other patients in 9.9%. Other associated characteristics included being male, recent diagnosis, living in a rural area and multiple somatic illnesses. However, multiple subsequent studies across differing countries show elevated rates with the standardized mortality ratio in PD in South Korea at 1.99 [12]; in Serbia [4] and the United Kingdom [13], the rate is five times higher than expected rates, and in the Netherlands an odds ratio of PD in those committing suicide via poisoning was 2.9 [14]. In a nationwide retrospective Danish cohort study from 1980 to 2016, the adjusted incidence rate ratio was elevated at 2.4 [15]. In a population-based cohort study using Taiwan's National Health Insurance and Taiwan Death Registry, the risk of suicide was elevated in PD (N = 35,891) (hazards ratio 2.1) relative to controls (N = 143,557) [16]. Suicides in PD were associated with younger age, urban dwelling, higher psychiatric rates, and often use of high lethality methods (jumping). The differences in rates may be related to cross-cultural differences in suicidal behavior, although multiple large-scale studies across multiple countries suggest elevated completed suicide rates relative to the general population. Taken together, suicidal ideation in PD is common, and completed suicides appear to be higher than the general population, although influenced by country.

Deep Brain Stimulation and Suicidal Outcomes

STN DBS appears to be associated with higher suicide outcomes in retrospective case-control studies but not in prospective randomized controlled trials. In a large international multicenter study reported in 2008 involving 55 centers, completed suicides occurred in 0.45% (24/5311) and attempted suicides in 0.9% (48/5311) [17]. Suicides occurring in the first postoperative year (0.26%) (263/100,000/year) were higher than the World Health Organization Standardized Mortality Ratio for suicide, age- and gender-matched (SMR: 12.63–15.64; $P < 0.001$), and remained elevated to the fourth postoperative year (0.04%) (38/100,000/year) (SMR: 1.81–2.31; $P < 0.05$) (Fig. 32.1). The excess number of deaths was 13 for the first postoperative year. Seventy-five percent of events occurred within the first 17 postoperative months. Postoperative mortality in the first year following STN DBS from other causes (e.g., hemorrhage, infection) has been reported at 0.41%. Thus, postoperative suicidal outcomes represent the highest risk for mortality following STN DBS.

A large single-center study of STN DBS patients, reported 10 years later in 2018, reported completed (0.75%, 4/543) and attempted (4.11%, 22/543) suicide rates [18]. The authors emphasize that the rate in the first (1/543), second, and third years were higher than the expected standardized mortality ratio. Those with ideation or

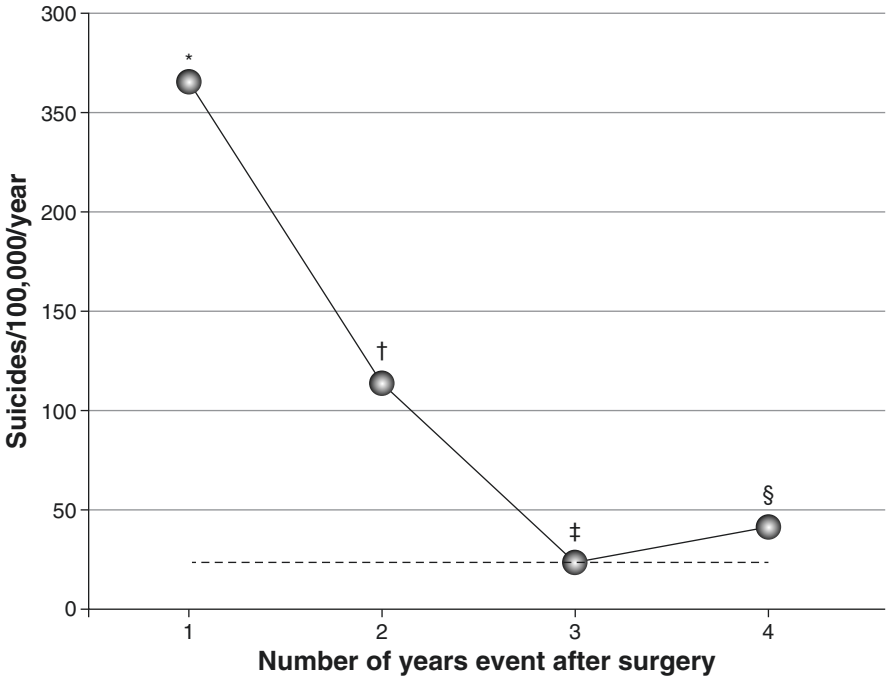

Fig. 32.1 Comparison of the suicide rate per postoperative year following subthalamic stimulation for advanced Parkinson's disease with the baseline suicide rate (printed with permission from Brain). *$P < 0.001$, weighted SMR = 12.64–15.64; †$P < 0.001$, weighted SMR = 5.13–6.91; ‡$P > 0.05$, weighted SMR = 0.91–1.16; §$P < 0.05$, weighted SMR = 1.81–2.31. The observed postoperative STN DBS suicide rates per 100,000/year (*solid line*) and the lowest (*gray dotted line*) and highest (*black dotted line*) age-, gender-, and country-adjusted WHO expected suicide rates per 100,000/year are reported. (Reprinted from Voon et al. [17], with permission from Oxford University Press)

attempting suicide after STN DBS showed greater psychotic symptoms, family psychiatric history, psychiatric medication use, and higher frontal and depression scores.

In contrast, a randomized DBS and medical control trial, Phase 1 with DBS ($N = 121$) versus 6 months of best medical therapy ($N = 134$) reported no suicidal behaviors with similar rates of new-onset suicidal ideation (1.9% and 0.9%) [19]. The Phase 2 trial randomized to STN ($N = 147$) or GPi ($N = 152$) showed similar rates of suicidal ideation (1.5% and 0.7%). In an open-label STN DBS randomized medication-controlled trial with early motor complications, over the 2-year period, 2/124 STN DBS and 1/127 died by suicide [20]. In subsequent meta-analyses of STN DBS patients involving four cross-sectional, four cohort, and two randomized controlled trials and two case-control trial studies, STN DBS had a higher odds ratio

but was not significantly higher relative to PD controls (OR = 2.84, $P = 0.18$) [21]. However, suicidal ideation and/or behaviors were significantly higher than the general population (lnSMR = 3.83, $P < 0.001$). Another meta-analysis including 18 studies showed the pooled rate of suicidal ideation was 4%, suicidal attempts 1%, and suicides 1% [22]. These conflicting results between retrospective clinical cohorts and prospective randomized trials are likely related to differences in comparator groups (medically treated PD versus general population), sample size, and duration of follow-up. Clinical trials will also more frequently follow up, inquire, and treat neuropsychiatric symptomatology with more careful follow-up relative to general clinical populations. Given the rare nature of suicides, smaller studies should be cautiously interpreted and may be influenced by reporting bias. The rate of suicide attempts in this PD clinical cohort may also be underreported or represent a greater proportion of successful attempts. The rates of completed suicides may also change over time given increased awareness of the issue and changes in preoperative and postoperative practices.

The rate of suicide is commonly elevated following any life-altering surgery. For instance, the suicide rate following epilepsy surgery is 1% or 31 times higher than the general population [23]. The baseline rate of suicide in epilepsy is eight times higher than the general population [24]. The study of associated behaviors allows us to address potentially modifiable risk factors. In a study of 200 STN DBS PD patients, 1/200 (1%) had completed and 4/200 (2%) had attempted suicides [25]. Suicidal behaviors were associated with postoperative depression and impaired impulse regulation in this study. Similarly, the multicenter study compared 27 attempted suicides and 9 completed suicides with 70 STN DBS controls selected from the patients who underwent surgery immediately prior to and immediately following the identified case at the same center [17]. Postoperative depression ($P < 0.001$), being single ($P = 0.007$), and a history of impulse control disorders or compulsive medication use ($P = 0.005$) were independent associated factors accounting for 51% of the variance of attempted suicide risk. Other associated factors included being younger, younger PD onset, and previous suicide attempt ($P < 0.05$). A trend was observed associated with greater changes in dopaminergic medications ($P = 0.05$). Overall, postoperative depression was the primary factor associated with both attempted and completed suicides after stringent correction for multiple comparisons. See Table 32.1 for a summary of factors associated with STN DBS for PD.

Postoperative depression following STN DBS has been associated with significant decreases in dopaminergic medications [26], a prior history of depression [27], and significant psychosocial postoperative changes [28] and has also been linked to serotonergic modulation in an animal model [29]. Possible effects of STN stimulation, dopaminergic medications, and the interaction between the two may also play a role in impulsivity.

Table 32.1 Summary of factors associated with attempted suicides following STN DBS for Parkinson's disease

	Probably associated ($P < 0.01$)	Possibly associated ($P < 0.05$)	Not associated ($P > 0.05$)	Unknown
Preoperative individual factors	Hx of impulse control disorders or compulsive medication use	Previous attempt Younger age Younger Parkinson's disease onset	Gender Preoperative cognitive status	Family history of suicide
Postoperative state	Postoperative depression[a] Postoperative apathy		Motor efficacy Stimulation parameters Postoperative cognitive changes	Interaction of stimulation with impulse control
Medication		Percent LEDD decrease**		Dopaminergic withdrawal state
Psychosocial factors	Single		Country-specific suicide rates	Expectations identity changes Relationship changes Supports other stressors

[a]Postoperative depression remains significant following Bonferroni correction. Reprinted from Voon et al. [17], with permission from Oxford University Press

**$P = 0.05$

Conclusion

Suicidal ideation is common in PD. Although completed suicides were once suggested to occur much less frequently than expected, large-scale studies across multiple countries suggests an elevated risk relative to the general population. Country-specific or cultural factors may play a modifying role. Suicidal behaviors in PD demonstrate a clear and consistent association with depression, thus highlighting the necessity to screen for and treat depressive symptoms along with actively screening for suicidal ideation in depressed patients. Other potential associated factors for suicide attempts include psychosis, impulse control disorders, younger age, and anxiety disorders. The early postoperative state following STN DBS poses an increased risk of suicide relative to the general population although whether this is elevated relative to matched medicated controls is less clear. Since suicidal behaviors are preventable and modifiable, careful assessment and education is indicated.

Suicidal behaviors correlate with depression in PD patients, and the early post-operative period following bilateral STN DBS is a period of increased risk.

Preoperative assessment should include a psychosocial assessment focusing on potential risk factors for suicide attempts, including being single and a previous history of impulse control disorders. Other possible factors include being younger, younger age of PD onset, and a history of previous attempts. Patients at higher risk should be counselled preoperatively along with family involvement and active postoperative follow-up. Preoperative psychoeducation should warn of the rare but possible risks with the goal of highlighting that these postoperative neuropsychiatric symptoms are treatable if recognized and adequately followed. Preoperative psychotropic medications should be maintained to avoid withdrawal states. Dopaminergic medication titration should be instituted with care to avoid the dopaminergic withdrawal state given its possible association with suicidal behaviors and potential liability with postoperative depression.

Patients and their caregivers should be questioned on neuropsychiatric behaviors and suicidal ideation in the postoperative period, particularly in the first 3 years after surgery. Patients with suicidal ideation or attempts should be referred to a psychiatrist. Issues of safety should be considered if a suicide attempt occurs, including the need for certification, hospitalization, and observation. The index of suspicion for postoperative depression should be high and those with depression carefully monitored and treated. The etiology of any postoperative depressive or apathy symptoms should be considered and may require resumption of the dopaminergic medication if related to the withdrawal state, or possibly resumption of a dopamine agonist or of other preoperative medications that may have been inadvertently discontinued such as benzodiazepines or antidepressants. A time-limited confusional state may require careful observation or possibly a low dose of an atypical neuroleptic. Hypomania can be managed with observation, if time limited and mild, or may require changes in dopaminergic medications or stimulation parameters. Psychosocial issues should be addressed including changes in relationships or identity and may require referrals for counselling or support.

Suicidal outcomes in PD represent a potentially modifiable form of mortality. Further studies to address modifiable risk factors would be useful for clinical management.

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