doi:10.1093/brain/awn214 Brain (2008), 131, 2720–2728

A multicentre study on suicide outcomes following subthalamic stimulation for Parkinson's disease

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Subthalamic nucleus deep brain stimulation improves motor symptoms and quality of life in advanced Parkinson's disease. As after other life-altering surgeries, suicides have been reported following deep brain stimulation for movement disorders. We sought to determine the suicide rate following subthalamic nucleus deep brain stimulation for Parkinson's disease by conducting an international multicentre retrospective survey of movement disorder and surgical centres. We further sought to determine factors associated with suicide attempts through a nested case-control study. In the survey of suicide rate, 55/75 centres participated. The completed suicide percentage was 0.45% (24/5311) and attempted suicide percentage was 0.90% (48/5311). Observed suicide rates in the first postoperative year (263/100 000/year) (0.26%) were higher than the lowest and the highest expected age-, gender- and country-adjusted World Health Organization suicide rates (Standardized Mortality Ratio for suicide: SMR 12.63–15.64; $P < 0.001$) and remained elevated at the fourth postoperative year (38/100 000/year) (0.04%) (SMR 1.81–2.31; $P < 0.05$). The excess number of deaths was 13 for the first postoperative year and one for the fourth postoperative year. In the case-control study of associated factors, 10 centres participated. Twenty-seven attempted suicides and nine completed suicides were compared with 70 controls. Postoperative depression ($P < 0.001$), being single ($P = 0.007$) and a previous history of impulse control disorders or compulsive medication use ($P = 0.005$) were independent associated factors accounting for 51% of the variance for attempted suicide risk. Attempted suicides were also associated ($P < 0.05$) with being younger, younger Parkinson's disease onset and a previous suicide attempt. Completed suicides were associated with postoperative depression ($P < 0.001$). Postoperative depression remained a significant factor associated with attempted and completed suicides after correction for multiple comparisons using the stringent Bonferroni correction. Mortality in the first year following subthalamic nucleus deep brain stimulation has been reported at 0.4%. Suicide is thus one of the most important potentially preventable risks for mortality following subthalamic nucleus deep brain stimulation for Parkinson's disease. Postoperative depression should be carefully assessed and treated. A multidisciplinary assessment and follow-up is recommended.

Keywords: suicide; deep brain stimulation; Parkinson's disease; depression; subthalamic stimulation

Abbreviations: ICDs = impulse control disorders; LEDD = Levodopa equivalent daily dose; SMR = standardized mortality ratio; STN DBS = subthalamic nucleus deep brain stimulation; UPDRS = Unified Parkinson's Disease Rating Scale

Received April 7, 2008. Revised June 23, 2008. Accepted July 19, 2008

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Introduction

Parkinson's disease is a neurodegenerative disorder characterized by motor, cognitive, behavioural, autonomic and other non-motor symptoms. The disorder can be treated by dopamine replacement therapy or neurosurgical therapies. Subthalamic nucleus deep brain stimulation (STN DBS) is a well-established surgical treatment effective for the motor symptoms and quality of life in advanced Parkinson's disease (Deuschl *et al*., 2006). However, postoperative neurobehavioural symptoms have been reported. These include depression (1.5–25%), (Houeto *et al*., 2002; Troster *et al*., 2003) hypomania/mania (4–15%), emotional reactivity (75%), postoperative confusion (0–25%), apathy (8–51%) (Czernecki *et al*., 2005; Castelli *et al*., 2006; Ory-Magne *et al*., 2007) and social difficulties (75%) (Schupbach *et al*., 2006) (for review see Voon *et al*., 2006). These neurobehavioural symptoms are possibly related to individual preoperative vulnerability, dopaminergic medication withdrawal, medication interacting with stimulation, postsurgical and stimulation effects, Parkinson's disease itself and psychosocial changes (Voon *et al*., 2006). However, the majority of these symptoms are transient and manageable.

Suicide rates following any significant life-altering events tend to be elevated. For instance, a recent meta-analysis of 11 epilepsy surgery studies reported a postoperative suicide rate of 1% which is 31 times higher than that of the general population (Pompili *et al*., 2006). The suicide rate following DBS for a range of movement disorders was reported at 4.3% (6/140) (Burkhard *et al*., 2004) and following globus pallidus internus DBS for dystonia at 12.5% (2/16) (Foncke *et al*., 2006). In one study, multiple surgeries and a history of severe depression appeared to be associated with suicidal outcomes (Burkhard *et al*., 2004). Other studies have reported suicide rates in Parkinson's disease patients following DBS at 0–1% (Krack *et al*., 2003; Albanese *et al*., 2005; Soulas *et al*., 2008), However, as these outcomes are rare, reports from either a single or a few number of centres may be subject to reporting bias.

Suicide is a major but largely preventable public health problem as identified by the World Health Organization (WHO) and is one of the top 10 causes of death (World Health Organization, 2006). Suicide is multifactorial in nature and results from a complex interaction of factors. A single factor is insufficient to be predictive as each factor accounts for a small proportion of the variance in risk and lacks specificity (Oquendo *et al*., 2006). Known suicide risk factors in the general population include psychiatric disorders and, in particular, depression, gender, age, marital status, comorbid physical illness and previous suicide attempts (Kessler *et al*., 1999; World Health Organization, 2006) (for review see Maris, 2002). In a recent study investigating risk factors in two completed and four attempted suicides from 200 STN DBS Parkinson's disease patients, suicidal behaviours were associated with postoperative depression and impaired impulse regulation (Soulas *et al*., 2008).

We performed a multicentre retrospective study with the following two objectives: (i) to determine the rate of postoperative attempted and completed suicides after STN DBS for Parkinson's disease and (ii) to determine factors associated with attempted suicides using a nested case-control follow-up study. Parkinson's disease patients having undergone DBS in other targets were not surveyed as the markedly smaller number of surgeries would have biased any comparisons.

Method

Study design

For the first objective to assess suicide rate, movement disorder and neurosurgical centres were contacted by phone and e-mail to ask if they would participate with contact attempted a minimum of three times. Inclusion criteria included centres with either a history of publications on DBS for Parkinson's disease or likely completion of more than 100 STN DBS surgeries. The number of STN DBS surgeries completed up to April 2005, the number of preoperative (while on the wait list) and postoperative attempted and completed suicides and the number of months the event occurred after surgery were requested.

For the second objective to assess factors associated with suicide attempts, centres with more than one event were asked if they would take part in a retrospective chart review using a specific questionnaire. Charts were reviewed either by a neurologist, psychologist, nurse or research assistant, who were part of the neurosurgical clinical or research team. Inclusion criteria for identified cases included either a reported completed suicide or attempted suicide. For each identified case, two Parkinson's disease controls without suicidal behaviours who had undergone STN DBS surgery immediately prior to and immediately after the identified case at the same centre were selected. All centres in the case-control study adhered to the commonly accepted selection criteria for surgery (Lang *et al*., 2006). Rates were compared to country-specific general population suicide rates (World Health Organization, 2006).

Suicide risk factors questionnaire

The following factors were compared between Parkinson's disease patients with suicide attempts and Parkinson's disease controls: gender, age, marital status, psychiatric disorders (pre-and postoperative depression were assessed categorically and dimensionally), previous suicide attempts, motor status, dopaminergic dose change and cognitive status.

The multiple-choice survey requested the following information:

(i) known suicide risk factors in the general population (Kessler *et al*., 1999; World Health Organization, 2006); for review see Maris (2002);
(ii) patient characteristics;
(iii) motor surgical outcome was assessed as percentage of postoperative motor improvement (last follow-up available) using the Unified Parkinson's Disease Rating Scale (UPDRS) motor score (Fahn *et al*., 1987), calculated as [(preoperative UPDRS motor score off-medication − postoperative UPDRS motor score off-medication/on stimulation)/preoperative UPDRS motor score off-medications] × 100. This variable

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was assessed to determine if motor efficacy of the surgical intervention was associated with suicide attempts;

(iv) electrical parameters (i.e. amplitude, frequency, pulse widths, contact polarity) and postoperative brain MRI for electrode placement confirmation were assessed to determine if DBS parameters or electrode placement was associated with attempts;

(v) preoperative and postoperative medication (at the time of the event) type and dose. Levodopa equivalent daily dose (LEDD) (Hobson *et al.*, 2002) percent change was calculated as (preoperative LEDD−postoperative LEDD)/preoperative LEDD. This variable was assessed to determine if a decrease in dopaminergic dose along with a potential dopaminergic withdrawal state was associated with attempts;

(vi) preoperative psychiatric status. To standardize preoperative depression reporting, a history of past depression included only patients on antidepressants at appropriate doses at the time of preoperative assessment. Preoperative depression assessment was based on Beck Depression Inventory (cut-off 14/15) (Visser *et al.*, 2006) or Montgomery Asberg Depression Rating Scale (cut-off 14/15) (Leentjens *et al.*, 2000) scores using Parkinson's disease-specific optimal cut-off scores. The Beck Depression Inventory is a 21-item patient-rated scale (score range 0–63) which has been validated in Parkinson's disease depression (Visser *et al.*, 2006). The Montgomery Asberg Depression Rating Scale is a 10-item clinician-rated scale (score range 0–70) which has been validated in Parkinson's disease depression (Leentjens *et al.*, 2000). The Parkinson's disease-specific optimal cut-off scores were used to dichotomize patients into depressed or not depressed in order to systematically assess for the presence or absence of depression as categorical variables. Impulse control disorders (ICDs) diagnosis was based on a history of clinician-diagnosed pathological gambling or hypersexuality. Symptoms of other ICDs such as binge eating or shopping had not been routinely assessed pro-operatively;

(vii) cognitive measures included the Mattis Dementia Rating Scale, Frontal Scores (Pillon *et al.*, 1986) and Mini Mental Status Exam scores were assessed to determine if cognitive status was associated with attempts. The Mini Mental Status Exam is a 30-point clinician-administered questionnaire that assesses for cognitive status. The Mattis Dementia Rating Scale is a clinician-rated instrument (range 0–144) for the assessment of cognitive status. The measures were compared as continuous variables;

(viii) postoperative behavioural symptoms included depression requiring antidepressant treatment, apathy, hypomania/mania, psychotic symptoms and hypersexuality recorded in the chart at any time after surgery. The symptoms of apathy, hypomania/mania, psychosis and hypersexuality were determined by clinical impression documented in the chart;

(ix) duration between last assessment and event; and

(x) outcomes included psychiatric treatment, type of treatment and degree of improvement.

All centres that participated in the data submission and chart review obtained approval or followed patient protection laws according to guidelines of their local hospital ethics boards.

Statistical analysis

The completed and attempted suicides were compared with age- and gender-matched country-specific suicide rate data from the WHO (World Health Organization, 2006) using Chi-Square test. To adjust for gender and age, the proportion of males undergoing DBS was presumed to be 65% (Hariz *et al.*, 2000) and the only the age ranges of 35–64 were considered. The highest and lowest expected number of suicides weighted per country were calculated as follows: Lowest expected number of age-, gender- and country-adjusted suicides per 100 000/year = Σ [[0.65 × (lowest suicide rate per 100 000 for men ages 35–64 per country) + 0.35 × (lowest suicide rate per 100 000 for women ages 35–64 per country)] × (number of surgeries per country−number of suicides from previous postoperative year per country)/total number of surgeries]. The same calculation was applied to determine the highest expected number of age-, gender- and country-adjusted suicides per 100 000/year. Both the highest and lowest expected number of suicides were reported. The observed number of suicides was calculated as follows: observed number of suicides per 100 000/year = observed number of suicides per year/(total number of surgeries−number of postoperative suicides in previous year) × 100 000. The weighted standardized mortality ratio (SMR) was calculated as follows: SMR = Σ [(observed number of suicides per country year/expected number of suicides per country year) × (number of surgeries per country/total number of surgeries)]. The excess number of suicides per year was calculated as follows: excess number of suicides = Σ [observed number of suicides per country−expected number of suicides per country].

The Mann–Whitney U-test for continuous variables and the Chi-Square test for discrete variables were used to compare associated factors between attempters and controls, completers and controls, postoperative depressed and non-depressed and postoperative apathetic and non-apathetic patients. Logistic regression analysis was used to determine independent risk factors for attempted suicide. For the comparison between factors associated with attempters and controls, a stringent correction for multiple comparisons was applied using the Bonferroni corrected $P < 0.003$. Statistics were calculated using SPSS 12.0.

Results

Suicide rates

Fifty-five centres completed the survey on suicide rates from 75 centres contacted (73%). Five thousand three hundred and eleven STN DBS patients were included. Nineteen North American (2189), 30 European (2787), one South American (110) and five Asian centres (225) participated.

The completed suicide percentage was 0.45% (24/5311) and attempted suicide percentage was 0.90% (48/5311). Centres had been performing STN DBS for mean 6.5 ± 1.7 years (range: 3–12). Three completed and three attempted suicides occurred on the wait list of patients approved for surgery; the total number of patients on the waiting list was not assessed. The mean wait list duration was 6.6 ± 7.8 months. The mean number of months after surgery of all events was 17.8 months (95% CI: 11.2–34.4) (range: completed suicides 1–48 months; attempted suicides 0.25–100 months). Fifty per cent of cases occurred by

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10 months and 75% by 17 months. The first postoperative year suicide rate (263/100 000/year) (0.26%/year) was significantly higher than the age- and gender-matched country-specific rates [SMR for suicide (based on the lowest and highest expected age- gender- and country-specific WHO suicide rates): SMR 12.63–15.64; $P<0.001$] and remained elevated at the fourth postoperative year (38/100 000/year) (0.04%) (SMR 1.81–2.31; $P<0.05$) (World Health Organization, 2006) (Table 1 and Fig. 1). The excess number of deaths was 13 for the first postoperative year and one for the fourth postoperative year. Participating countries were dichotomized into countries with high and moderate rates according to age-matched WHO suicide rates (World Health Organization, 2006). Countries with high baseline rates (>13/100 000/year) had a percentage of 0.59% (12/2037) and the countries with moderate baseline rates (6–13/100 000/year) had a percentage of 0.37% (12/3274). Postoperative percentages per country and country-specific suicide rates were not correlated (Pearson correlation coefficient = 0.30; $P=0.31$).

Associated factors

Ten centres were involved in the case-control study on associated factors. Twenty-seven attempted suicides and nine completed suicides were compared to 70 controls (Table 2). Attempted suicides were associated with being single, previous history of impulse control disorders or compulsive medication use, and postoperative depression. Attempted suicides were also more weakly associated with being younger, earlier Parkinson's disease onset, previous suicide attempt and percent LEDD change. Using logistic regression analysis, postoperative depression (P-value on model entry: $P=0.001$), being single ($P=0.001$), history of impulse control disorders ($P=0.002$) were independent factors accounting for 51% attempted suicide risk variance with an 82.5% prediction accuracy. Following correction for multiple comparisons, only postoperative depression remained significantly associated with attempted and completed suicides.

Almost half of patients verbalized suicidal ideation prior to attempts or completed suicides (Table 3).

Postoperative depression and apathy were the two behaviours seen most frequently at the time of suicide

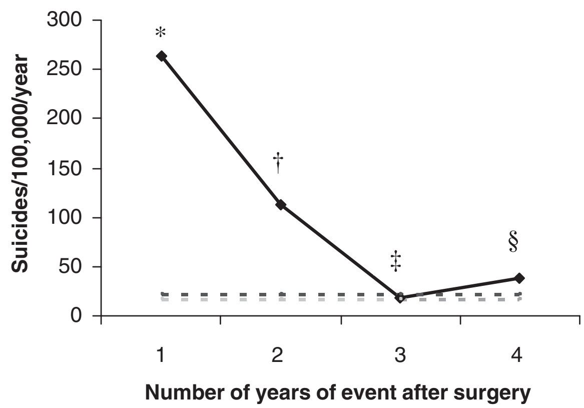

Fig. 1 Comparison of the suicide rate per postoperative year following subthalamic stimulation for advanced Parkinson's disease with the baseline suicide rate. *$P<0.001$, weighted SMR = 12.64–15.64; †$P<0.001$, weighted SMR = 5.13–6.91; ‡$P>0.05$, weighted SMR = 0.91–1.16; §$P<0.05$, weighted SMR = 1.81–2.31. The observed postoperative STN DBS suicide rates per 100 000/year (solid line) and the lowest (grey dotted line) and highest (black dotted line) age-, gender- and country-adjusted WHO expected suicide rates per 100 000/year are reported.

Table 1 Standardized mortality ratios per postoperative year for suicides following STN DBS for Parkinson's Disease

Postop year	Observed suicides per year	Observed suicides per 100 000/year[a]	Expected suicides per 100 000 year[b]	Weighted standardized mortality ratio[c]	95% CI	P-values	Excess number of suicides[d]
1	14	263.60	16.44	15.64	(9.81–26.32)	<0.0001	13.12
			20.92	12.63	(8.12–19.65)	<0.0001	12.88
2	6	113.27	16.44	6.91	(4.14–11.53)	<0.0001	5.13
			20.92	5.13	(3.42–8.62)	<0.0001	4.88
3	1	18.90	16.44	1.16	(0.61–2.22)	0.58	0.13
			20.92	0.91	(0.49–1.68)	0.87	−0.11
4	2	37.81	16.44	2.31	(1.30–4.09)	0.004	1.13
			20.92	1.81	(1.07–3.08)	0.03	0.89

One patient not included as duration after surgery was not reported.
[a]Observed number of suicides per 100 000 year = Observed number of suicides per year/(Total number of surgeries − Number of suicides in previous years) × 100 000. [b]Reported for lowest (top) and highest (bottom) age-, gender- and country-adjusted suicide rates. Lowest expected number of age-, gender- and country-adjusted suicides per 100 000 year = Σ [[0.65 × (lowest suicide rate 100 000 for men ages 35 to 64 country) + 0.35 × (lowest suicide rate 100 000 for women ages 35 to 64 country)] × (number of surgeries per country − number of suicides from previous postoperative year per country)/total number of surgeries]. The same calculation was applied to determine the highest expected number of age-, gender- and country-adjusted suicides per 100 000 year. [c]Weighted standardized Mortality Ratio (SMR) = Σ [(Observed number of suicides per country year/Expected number of suicides per country year) × (number of surgeries per country/total number of surgeries)]. P-values and 95% CI were obtained using chi-square analysis for the odds ratio or SMR. [d]Excess number of suicides = Σ [Observed number of suicides per country − Expected number of suicides per country].

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attempt (Table 3). Postoperative depressed patients ($n=48$) as a group had a greater frequency of preoperative antidepressant use ($n=39$) (32/48 versus 9/39; $P=0.03$) with a trend towards more frequent preoperative suicide attempts (7/47 versus 1/39; $P=0.07$). Postoperative apathetic patients ($n=15$) as a group had a greater frequency of postoperative depression (13/15 versus 33/70; $P=0.009$), preoperative history of impulse control disorders and compulsive medication use (6/15 versus 9/66; $P=0.03$), and greater percent LEDD change [mean (SD): 72.5% (19.1) versus 59.4% (30.2); $P=0.04$].

Discussion

Suicide rates

In this multicentre international retrospective survey involving 55 centres and 5311 patients, the percentage of patients committing suicide following STN DBS surgery for Parkinson's disease was 0.5% and that of attempted suicide was 0.9%. STN DBS had been performed at these centres between 3 and 12 years. Seventy-five percent of events occurred within the first 17 postoperative months. The age-matched SMR for suicide in the first postoperative year was 12.6–15.6 and decreased to 2.31–1.81 by the fourth

Table 2 Factors associated with postoperative attempted and completed suicides compared with controls following STN DBS for Parkinson's disease

	Number of controls	Control scores	Number of attempters	Attempters scores	*P*-Value (attempters versus controls)	Completers ($n=9$)
Patient characteristics						
Gender (% male)	70	50.0	27	59.0	0.31	56
Mean age in mean years ±95%CI	68	59.1 ± 2.1	24	52.9 ± 3.5	0.01	60.0 ± 7.8
Single	65	18.5 (12)	23	56.5 (13)	0.007	22.2 (2/9)
Age of Parkinson's disease onset in mean years ±95%CI	68	44.2 ± 2.0	24	38.5 ± 2.9	0.02	47.1 ± 8.4
Parkinson's disease duration in mean years ± 95%CI	68	15.1 ± 1.6	24	13.3 ± 2.1	0.21	12.9 ± 1.1
Preoperative UPDRS III off-meds mean ± 95%CI	67	48.8 ± 4.1	21	50.6 ± 5.9	0.65	52.8 ± 12.5
Preoperative LEDD mean in mg/d ± 95%CI	66	1273.5 ± 162.2	23	1391.7 ± 267.9	0.46	1374.4 ± 382.5
Preop psych hx						
Antidepressant use	69	33.3 (23)	24	37.5 (9)	0.83	33.3 (3/9)
BDI/MADRS scores above cutoff[a]	56	33.9 (19)	22	45.5 (10)	0.47	42.8 (3/7)
Past hx impulse control disorders or compulsive medication use	64	7.8 (5)	22	40.9 (9)	0.005	11.1 (1/9)
Previous suicide attempt	66	3.0 (2)	24	20.8 (5)	0.016	11.1 (1/9)
Postop motor and medication changes						
Percent UPDRS III motor change, mean ± 95%CI	67	50.7 ± 7.0	21	55.6 ± 12.4	0.43	N/A
Percent LEDD change, mean ± 95%CI	66	54.9 ± 7.4	23	63.9 ± 16.8	0.05	50.8 ± 19.7
Postop behaviour changes						
Postop depression	56	39.3 (22)	24	83.3 (20)	<0.0001	87.5* (7/8)
Postop Apathy	55	9.1 (5)	24	41.7 (10)	0.004	14.3
Cognitive status						
Preop Mattis Dementia Rating Scale, mean ± 95%CI	56	137.5 ± 1.5	19	138.0 ± 2.2	0.71	NA
Preop Frontal score, mean ± 95%CI	35	43.0 ± 2.3	15	41.0 ± 4.9	0.41	NA
Preop MMSE, mean ± 95%CI	11	28.8 ± 0.9	3	28.6 ± 1.5	0.67	NA
Postop Mattis Dementia Rating Scale, mean ± 95%CI	41	136.2 ± 2.1	17	134.6 ± 4.2	0.47	NA
Postop Frontal score, mean ± 95%CI	33	44.4 ± 6.7	14	38.9 ± 6.8	0.35	NA
Postop MMSE, mean ± 95%CI	11	27.2 ± 2.1	3	27.3 ± 3.5	0.95	NA

Reported in categorical variables of % (*N*) unless otherwise specified as mean ± 95% CI Scores reported for factors with <20% 'unknown' or incomplete.
[a]BDI and MADRS scores were dichotomized into categorical variables for the absence and presence of depression based on optimal Parkinson's disease-specific cut-off scores.
*$P<0.001$ of completed suicides compared with controls.
M = male; F = female; SD = standard deviation; hx=history; BDI = Beck Depression Inventory; MADRS = Montgomery Asberg Depression Rating Scale; postop = postoperative; MMSE = Mini Mental Status Exam; NA = not available.

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Table 3 Characteristics and outcomes of attempted and completed suicides following STN DBS for Parkinson's disease

	Attempted suicide	Completed suicide
Verbalized suicidal ideation	45.0 (9/20)	50.0 (5/10)
Mean duration between last assessment and event in days (SD)	89.8 (200.5)	23.3 (18.9)
<1 week	26.0 (6/23)	37.5 (3/8)
1 week to 1 month	21.7 (5/23)	50.0 (4/8)
1–3 months	39.1 (9/23)	12.5 (1/8)
3–6 months	4.3 (1/23)	0 (0/8)
>6 months	8.7 (2/23)	0 (0/8)
Stressors		
Separation/divorce	26.3 (5/19)	
Social isolation	10.5 (2/19)	
Placement	10.5 (2/19)	
Psychiatric diagnosis at time of attempt		
None	16.7 (4/24)	
Depression	45.8 (11/24)	
Psychotic symptoms	16.7 (4/24)	
Hypomania	4.2 (4/24)	
Apathy	41.7 (10/24)	
Levodopa withdrawal	8.3 (2/24)	
Generalized anxiety or panic attacks	20.8 (5/24)	
Adjustment disorder	20.8 (5/24)	
Treatments following events		
None	12.0 (3/25)	
Antidepressants	60.0 (15/25)	
Dopaminergic medication change	20.0 (5/25)	
Antipsychotics	16.0 (4/25)	
Psychotherapy	32.0 (8/25)	
Current status		
Not improved	4.3 (1/23)	
Somewhat improved	26.1 (6/23)	
Moderately improved	17.4 (4/23)	
Significantly improved	47.8 (11/23)	

Reported in % (*N*) unless specified.

postoperative year. This rate is considerably lower than the 4.3% (6/140) reported following DBS for a range of movement disorders at a centre that had performed DBS for 9 years (Burkhard *et al*., 2006). Four of six patients with completed suicides in this previous study were STN DBS Parkinson's disease patients. Within the general population suicide attempts are 20 times more frequent than completed suicides (World Health Organization, 2006). That the attempt rate was only twice that of the completed rate suggests either under-reporting or a greater proportion of successful attempts.

As further comparison, the suicide rate following epilepsy surgery is 1% or 31 times higher than the general population (Pompili *et al*., 2006). However, whereas the baseline epilepsy suicide rate is eight times higher than the general population (Pompili *et al*., 2005), baseline Parkinson's disease suicide rates range from the same as to as much as 10 times lower than the general population (Myslobodsky *et al*., 2001; Juurlink *et al*., 2004), despite the presence of a chronic medical illness, comorbid psychiatric disorders and psychosocial losses. Thus, the relative postoperative suicide rate may be greater for Parkinson's disease than for epilepsy. Furthermore, postoperative mortality from other causes (e.g. haemorrhage, infection) in the first year following STN DBS for Parkinson's disease was reported at 0.41% (3/737) (Hamani *et al*., 2005). Thus, suicide in the first postoperative year (0.26%) represents one of the highest potentially modifiable risks for mortality following DBS for Parkinson's disease.

Limitations of our study include its retrospective nature, differential followup at centres, lack of systematic diagnostic criteria and sample size in the case-control study. However, the use of rating scales, appropriate Parkinson's disease-specific cutoff scores for depression severity and a definition of clinical severity of depression based on need for treatment limited subjective reporting. The inclusion of centres was restricted based on criteria that would capture centres with adequate postoperative follow-up to ensure a valid reporting of postoperative suicide rates. However, we note that this may create a sampling bias since highly subspecialized centres with adequate follow-up would have lower suicide rates. Furthermore, the dropout rate during follow-up is a significant issue, which is not quantified in this paper. Finally, events occurring in the later postoperative years were likely under-reported. Thus, the rates reported in this study are likely an underestimate of the actual rate.

That the Parkinson's disease suicide rate is similar or lower than the general population allows for the general population baseline suicide rate to be used as a comparator. However, we note that suicide rates are likely higher in those presenting for surgery as reflected in the observed events on waiting lists (three attempted and three completed suicides). Patients presenting for surgery likely have different motivations for surgery, coping strategies, age and disease burden. For instance, a history of repeated surgeries was previously identified as a risk factor (Burkhard *et al*., 2004). A wait-list control group would be more appropriate control (Voon *et al*., 2006).

Associated factors

The primary risk factors associated with suicide attempts in this study were related to known general suicide risk factors and postoperative behavioural states (summarized in Table 4). A trend of greater changes in postoperative dopaminergic medication dose ($P = 0.05$) was observed with suicide attempts. Attempts were not associated with motor outcome. Missing data may contribute to biases.

Completed suicides in the general population are associated with a psychiatric disorder, particularly depression (World Health Organization, 2006). In this study, post-operative depression was associated with both completed and

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Table 4 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.
**$P = 0.05$.

attempted suicides after STN DBS. These findings are in keeping with the observation that postoperative depression following STN DBS has a greater effect on quality of life than motor outcomes (Troster *et al.*, 2003). Postoperative depression can be related to the psychosocial changes, the neurobiology of Parkinson's disease, the dopaminergic withdrawal state or individual vulnerabilities. This finding is consistent with a recent study demonstrating that suicidal behaviours was associated with postoperative depression (Soulas *et al.*, 2008). Our ability to identify risk factors for completed suicides was limited by the small sample size.

Attempted suicides in the general population are associated with depression, substance abuse, divorce and being female (World Health Organization, 2006). In this current study, postoperative suicide attempts were associated with postoperative depression, being single, and a history of impulse control disorders or compulsive medication use. Other weaker associations included younger age, younger Parkinson's disease onset and preoperative suicide attempts. There were no significant associations with gender or preoperative depression. Eighty percent had postoperative psychiatric diagnoses. Forty-seven percent had a major relationship or residential change or were socially isolated. These findings are in keeping with recent studies focusing on psychosocial issues suggest a high proportion of marital difficulties (75%) following STN DBS surgery (Schupbach *et al.*, 2006). Expectations, identity changes, more subtle relationship changes and other psychosocial losses were not assessed.

Medication-induced impulse control behaviours and compulsive dopaminergic medication use can be improved by STN stimulation and medication decreases in well-selected Parkinson's disease patients (Ardouin *et al.*, 2006). However, new onset pathological gambling has been reported after STN DBS (Smeding *et al.*, 2007). Our study suggests Parkinson's disease patients with a history of these behaviours may be at greater risk for postoperative suicide attempts.

Although country-specific baseline suicide rates differ, there was no significant association with country-specific suicide rates and STN DBS suicide outcomes. However, the cultural willingness to report suicide outcomes and the acceptance of 'rational suicide' may be confounders.

Patients with preoperative depression and antidepressant use or previous suicide attempts were more likely to develop postoperative depression, thus highlighting the importance of obtaining a preoperative psychiatric history (Houeto *et al.*, 2002). Although postoperative depression and apathy were correlated, the behaviours were dissociable in this study. Whereas postoperative depression was associated with markers of preoperative depression, apathy was associated with a history of impulse control disorders and greater dopaminergic dose decrease.

Finally, a greater LEDD decrease was weakly associated with suicide attempts suggesting that the relative LEDD change may unmask underlying behavioural states or mediate dopaminergic withdrawal symptoms leading to postoperative depression or apathy.

High lethality suicide attempts in the general population have been associated with impairments in the Stroop interference task (a measure of the ability to suppress irrelevant responses and a marker of impulsivity) (Keilp *et al.*, 2001) and in verbal fluency (Keilp *et al.*, 2001), both of which can be impaired by STN stimulation (Voon *et al.*, 2006). However, rather than specific impairments, higher lethality suicide attempts have been suggested to be associated with greater generalized executive impairments

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(Keilp *et al.*, 2001) and decreased prefrontal cortical activity (Oquendo *et al.*, 2003). In our study, general measures for executive and cognitive scores did not differ between attempters and controls. Specific tests for verbal fluency and the Stroop task were not systematically conducted.

Impulsive suicide attempts have also been considered a form of impulsive behaviour. Impulsive behaviour can be subdivided into three different forms: motoric impulsivity (or the inability to inhibit a prepotent motor response), the tendency to rapid decision making without adequate evaluation of choices or impulsive choice (or the tendency to devalue delayed rewards). The effects of STN DBS on the first two factors have been assessed. STN stimulation has been demonstrated to improve both choice reaction time and response inhibition as measured using the stop-signal task (van den Wildenberg *et al.*, 2006). The authors suggest that the results are due to the overall improvement of parkinsonian symptoms rather than a specific effect of STN stimulation on response selection and inhibition. However, Hershey *et al.* (2004) demonstrated that motor response inhibition was impaired with a go/no-go task in the context of higher cognitive demand. Several, but not all, studies have demonstrated STN stimulation induced impairments in a task that requires response inhibition and response selection during high conflict (Stroop word–colour interference task) (reviewed in Voon *et al.*, 2006). Frank *et al.* (2007) further demonstrated that STN stimulation in Parkinson's disease patients results in faster reaction times to high conflict rewarding choices rather than the expected slowing of decision making. This effect was not seen with high conflict punishment choices. Thus, the literature suggests that STN stimulation does not affect motor impulsivity but impairs decision making under conditions of high conflict rewarding choices. However, as decision making in suicidal outcomes is likely associated with conflicting choices involving punishment avoidance, it is not clear if the cognitive impairments observed with STN stimulation are necessarily related to suicidal behaviours.

In conclusion, postoperative suicide is one of the most important and potentially preventable risks for mortality following STN DBS for Parkinson's disease. We demonstrate that the risk is significantly elevated in the first postoperative year and remains elevated in the fourth postoperative year. Our data are likely an underestimate of the true risk particularly in the late postoperative years. The risk, like that in the general population, is multifactorial. No single factor is sufficient to predict risk or should serve as a surgical contraindication. Postoperative depression should be followed and managed. Subjects with a history of impulse control disorders or compulsive medication use and are single may be at higher risk for suicide attempts and should be carefully assessed and followed. Patients should be encouraged to be open during preoperative assessment with the understanding that the assessment is multifactorial with the goal to identify factors requiring management and closer follow-up. Patients and family members should be warned of this potential outcome. Clinicians should actively inquire about suicidal ideation and promote awareness that the symptom is treatable. Suicidal ideation should be taken seriously. A multidisciplinary assessment and follow-up is encouraged.

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Appendix

The prevalence rates were presented at an oral session at the American Academy of Neurology, San Diego, USA, 2006. The associated factors were presented at an oral session at the Movement Disorders Congress, Kyoto, Japan, 2006. The following Investigators participated in the study: (i) Asia: India, Kerala: A. Kishore, RM Rao; Japan: Tokyo: Y. Katayama, K. Osaka, Y. Suzuki, T. Yamani; Nagano: T. Hashimoto, T. Goto; Malaysia, Sunway: C-P. Chee, F-C. Lee, M-K Lee; Taiwan, Hualien: S-Y Chen, S-H Lin; Thailand, Bangkok: A. Pisampong; (ii) Europe: Austria, Innsbruck: G. Wenning, E. Wihelm. E. Wolf; Vienna: F. Alesh, T. Brucke, D. Voic; Belgium, Gent: P. Santens, J. Caemaert; Denmark, Aarhus: K. Ostergaard, N. Sunde; France: Clermont-Ferrand: F. Durif, JJ. Lemaire; Grenoble: A-L. Benabid, V. Fraix, P. Pollak; Lille: S. Blond, P. Krystkowiak; Lyon: E. Broussolle, P. Mertens, S. Thobois, J. Xie-Brustolin; Marseille: JP. Azulay, JC. Peragot, J. Regis, Witjias; Nantes: P. Damier, S. Raoul; - Paris: AM. Bonnet, P. Cornu; Germany: Berlin: A. Kupsch, GA. Schneider, T. Trottenberg; Kiel: B. Moller, J. Reiff, HM. Mendom; Munich: K. Boetzel, U. Steude; Italy: Ancona: MG. Ceravolo, M. Scerrati Milan: A. Albanese, E. Caputo, M. Egidi, A. Franzini, L. Romito; Monza: A. Antonini, A. Landi, Rome: P. Mazzone, A. Peppe, P. Stanzione; Turin: M. Lanotte, L. Lopiano; Spain: Barcellona: J. Rumia, F. Valldeoriola; Madrid: J. Ayerbe, JM. de Igneson, P. Garcia-Ruiz Espiga; - Pamplona: J. Guridi,J. Obeso, M. Oroz-Rodriguez; - San Sebastian: G. Linazasoro, E. Ramos, N. Van Blercom; The Netherlands, Amsterdam: PR Schuurman, HM Smeding; United Kingdom: London: P. Dowsey-Limousin, M. Hariz, M. Samuel; Oxford: T. Aziz, P. Bain; (iii) North America: U.S.A.: Arizona, Phoenix: D. Lieberman, P. Mahant, A. Shetter, K. Smith; California, San Francisco: W. Marks, P. Starr; Colorado, Englewood: R. Kumar; Florida; Gainesville: KD. Foote, M. Okun; Florida, Jacksonville: R. Uitti, R. Wharen; Kansas, Kansas City: K. Lyons, R. Pahwa, SB. Wilkinson; Minnesota, Minneapolis: RE. Maxwell, P. Tuite; Missouri, St. Louis: JS. Perlmutter, FJ. Revilla, SD Tabbai; Pensillvania, Philadelphia: G. Baltuch, G. Duda, G. Kleiner-Fisman, M. Stern; Texas, Houston: W. Ondo, R. Simpson; Wisconsin, Madison: C. Garell, E. Montgomery; Ohio, Cleveland: M. Giroux, A. Rezai, J. Vitek; New York, New York: R. Alterman, M. Tagliati (Mount Sinai Hospital), B. Ford, D. Hardesty (Columbia University); Illinois, Chicago: J. Rosenov, T. Simuni (Northwest University), J. Collzens, T. Eller, S. O'Leary, M. Rezak (Evanston Northwest Healthcare), L. Verhagen (Rush University Medical Center); Providence, Rhode Island: K. Chou, G. Friehs; (iv) South America: Argentina, Buenos Aires: A. Antico, M. Merello.

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