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Suicide ideation and behaviours after STN and GPi DBS surgery for Parkinson's disease: results from a randomised, controlled trial

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Abstract

Background—The risk of suicide behaviours post–deep brain stimulation (DBS) surgery in Parkinson's disease (PD) remains controversial. We assessed if suicide ideation and behaviours are more common in PD patients (1) randomised to DBS surgery versus best medical therapy (BMT); and (2) randomised to subthalamic nucleus (STN) versus globus pallidus interna (GPi) DBS surgery.

Methods—In Phase 1 of the Veterans Affairs CSP 468 study, 255 PD patients were randomised to DBS surgery (n=121) or 6 months of BMT (n=134). For Phase 2, a total of 299 patients were randomised to STN (n=147) or GPi (n=152) DBS surgery. Patients were assessed serially with the Unified Parkinson's Disease Rating Scale Part I depression item, which queries for suicide ideation; additionally, both suicide behaviour adverse event data and proxy symptoms of increased suicide risk from the Parkinson's Disease Questionnaire (PDQ-39) and the Short Form Health Survey (SF-36) were collected.

Results—In Phase 1, no suicide behaviours were reported, and new-onset suicide ideation was rare (1.9% for DBS vs 0.9% for BMT; Fisher's exact $p=0.61$). Proxy symptoms of relevance to suicide ideation were similar in the two groups. Rates of suicide ideation at 6 months were similar for patients randomised to STN versus GPi DBS (1.5% vs 0.7%; Fisher's exact $p=0.61$), but several proxy symptoms were worse in the STN group.

Conclusions—Results from the randomised, controlled phase of a DBS surgery study in PD patients do not support a direct association between DBS surgery and an increased risk for suicide ideation and behaviours.

INTRODUCTION

Parkinson's disease (PD) is a chronic, disabling neurodegenerative disease, and deep brain stimulation (DBS) is increasingly used as a treatment option for patients who experience complications of standard pharmacological treatment.¹ The most common lead location for DBS surgery in PD patients is bilateral subthalamic nucleus (STN), but bilateral globus pallidus interna (GPi) is also used, and previous research has suggested similar motor effects for the two locations, but perhaps better non-motor effects for the GPi location.²³

PD is characterised by frequent occurrence of a range of non-motor symptoms, including depression.⁴ Although depression is relatively common in PD, and depression is the primary risk factor for suicide completion in the general population,⁵ limited research has suggested that completed suicide is uncommon in PD.⁶⁷ However, in recent research we found that current suicide ideation (a predictor of suicide attempts⁸⁹) was present in 11% of PD patients with increasing severity of depressive symptoms, the only predictor of suicide or death ideation on multivariable analysis.¹⁰

The association between DBS surgery and suicide behaviours (ie, hereafter defined as either suicide attempts or suicide completion) remains controversial. Case reports and observational studies, often with long-term follow-up, have suggested that DBS leads to suicide attempts or completed suicide in a subset of PD patients.^{11–13} In a retrospective survey of a large number of PD patients undergoing DBS surgery, the 4-year attempted or

completed suicide frequency was 1.4%, which the authors concluded was elevated compared with the general population based on epidemiological data.¹⁴ However, this study data was retrospective, not all invited sites participated in the study, and there were no active control groups to directly support the claim of increased risk.

The Department of Veterans Affairs Cooperative Studies Programme 468 study (CSP 468) was a multisite, randomised, controlled study of DBS surgery for the motor symptoms of PD. In Phase 1, conducted from 2002–2006, patients were randomised to 6 months of DBS surgery versus best medical therapy (BMT).¹⁵ In Phase 2, which included patients participating in Phase 1 as well as additional subjects, patients undergoing STN versus GPi DBS surgery were compared and followed long term (24-month results presented in the primary manuscript).² Of note, there was no depression exclusion criterion for the study, and baseline Beck Depression Inventory-II (BDI)¹⁶ scores were typical for a PD population receiving specialty care,¹⁷ with 20% of patients entering Phase 1 exceeding recommended cut-off scores for a diagnosis of depression.¹⁵¹⁸ In addition, there was no difference in depression severity between the DBS surgery and BMT treatment groups at either baseline or 6 months,¹⁵ but the GPi group was less depressed at 24 months compared with the STN group based on the BDI score.²

Using both a depression item that included a response for suicide ideation and adverse event data, we calculated the frequency of suicide ideation and suicide behaviours post-DBS surgery in the CSP 468 study. Comparisons were made between the DBS surgery and BMT groups for the 6-month controlled phase, as well as between the STN and GPi DBS surgery groups out to 2 years. In addition, as there are known correlates of suicide behaviours in addition to suicide ideation (eg, depression, other psychiatric symptoms (including anxiety), and hopelessness⁵), we also analysed other available post-DBS surgery non-motor symptom data that might serve as proxy symptoms of increased risk for suicide ideation and behaviours. We hypothesised that PD patients undergoing DBS surgery, compared with a PD control group receiving BMT, would have similar frequencies of suicide ideation and behaviours in the 6-month period post-DBS surgery.

MATERIALS AND METHODS

Participants

The methods for CSP 468 have been published previously.²¹⁵ In Phase 1, 255 patients underwent randomisation to DBS surgery (n=121) or BMT (n=134),¹⁵ and for Phase 2, a total of 299 patients were randomised to STN (n=147) versus GPi (n=152) DBS surgery, with data presented for two years of follow-up for the primary manuscript.²

Standard protocol approvals, registrations and patient consents

The study was approved by each site's institutional review board and patients provided written informed consent.¹⁵

Assessment instruments

Although suicide ideation was not formally queried as part of study assessments, for the purposes of this study, its presence was determined based on the response to the Part I depression item of the Unified Parkinson's Disease Rating Scale (UPDRS),¹⁹ administered and rated by an experienced PD research coordinator. The highest level response for this 5-point Likert item is 'sustained depression with vegetative symptoms *and suicidal thoughts or intent*.' Phase 1 and 2 participants were assessed with this item at baseline (for Phase 1 they were assessed before they learned of the outcome of their randomisation to DBS surgery or BMT), month 3 and month 6 (the latter being the end of controlled Phase 1). Phase 2 participants also completed this assessment at months 12 and 24.

For the purposes of this manuscript, suicide behaviour was considered to be a suicide attempt that resulted in hospitalisation or death (ie, a serious adverse event). Formal adverse event queries were made at in-person visits at months 3, 6 (Phases 1 and 2), 12 and 24 (Phase 2 only), and spontaneous adverse event reporting occurred ad hoc.

Other current psychological and psychiatric symptoms of potential relevance to the development of suicide ideation and behaviours were selected prior to any analyses by one of the authors (DW) from the 39-item Parkinson's Disease Questionnaire (PDQ-39)²⁰ and the Short Form Health Survey (SF-36).²¹ From the PDQ-39, the items selected were: 'felt depressed', 'felt isolated and lonely', 'felt weepy or tearful', 'felt angry or bitter', 'felt anxious', 'felt worried about your future', 'felt your memory was failing' and 'had distressing dreams or hallucinations'. PDQ-39 items are scored on a 1- to 5-point Likert scale, and for the purposes of these analyses a positive response was considered a choice of 'always' or 'often' (the two most impaired ratings on the Likert scale). For the SF-36, the items selected were: 'how much bodily pain', 'feel full of life', 'been very nervous', 'felt so down in dumps that nothing could cheer you up', 'felt calm and peaceful', 'have a lot of energy', 'felt downhearted and depressed', 'feel worn out', 'been happy', 'feel tired' and 'expect health to get worse'. The SF-36 also uses a 5-point Likert scale for the items that were selected, and a positive response was considered a choice of either 'very severe', 'severe' or 'moderate' (pain); 'definitely true' or 'mostly true' (expect health to get worse); or 'all of the time' or 'most of the time' (all other items). Participants were assessed with the PDQ-39 and the SF-36 at baseline and at months 6, 12, 18 and 24.

Statistical analysis

χ^2 and Fisher's exact test were used for comparisons between treatment groups. To control for baseline response on the PDQ-39 and SF-36, the Cochran–Mantel–Haenszel statistic was used to assess association between 6-month response and treatment group assignment for those variables with baseline differences. Analyses were conducted using SAS software V. 9.2; tests were two-tailed and significant at $p < 0.05$ and trend at $p < 0.10$, and no formal corrections were made for multiple analyses.

RESULTS

Participant randomisation and dropouts during controlled phase

Of the 255 participants who were randomised to DBS surgery or BMT, 224 (87.8%) had 6-month study visit data available for the UPDRS Part I depression item (DBS=108, BMT=116). Reasons for missing evaluations at the end of randomised phase (n=31) were (descending order of frequency): withdrawal of consent (n=13), withdrawal due to medical complications (n=7, including 5 who never underwent DBS surgery), administrative withdrawal when BMT group closed (n=6), withdrawal due to randomisation to BMT group (n=2), and missed visit (n=2), and death (n=1) (figure 1). The discontinuation due to death was not a completed suicide or related to a suicide attempt.

In the entire sample, except the six patients who were administratively withdrawn, participants who withdrew prior to the completion of the controlled phase or missed the 6-month visit were older (67.2 vs 61.9 years, $p=0.004$), had longer PD duration (15.7 vs 11.9 years, $p=0.04$), and were more likely to be women (40.0% vs 15.6%, $p=0.006$), with no differences in baseline Beck Depression Inventory (BDI) score or total levodopa equivalent daily dosage (LEDD) (data not presented). Examining by randomised group, women were more likely to drop out in the BMT group only ($p<0.001$), increasing age was associated with discontinuation in the DBS surgery group only ($p<0.001$), and PD duration was not associated with study discontinuation in either subgroup ($p=0.06$ (DBS) and $p=0.31$ (BMT)).

New-onset suicide ideation and behaviours during controlled phase of DBS versus BMT

At baseline, no patients in either group reported suicide ideation based on their response on the UPDRS Part I depression item (table 1). Likewise, at month 3, no patients expressed suicide ideation. At month 6, new-onset suicide ideation was rare with no between-group differences (1.9% for DBS vs 0.9% for BMT), with both DBS surgery patients experiencing new-onset suicide ideation randomised to the STN location. Based on adverse event data, no suicide behaviours were reported in either the DBS surgery or BMT groups during the entire randomised phase.

For the two DBS surgery patients who reported new-onset suicide ideation at month 6, one had baseline and month 6 BDI scores of 21 and 26; the other had baseline and month 6 BDI scores of 22 and 34. The baseline BDI scores for both of these patients were above the diagnostic cut-off point for depression.¹⁸ One patient had baseline total (levodopa +dopamine agonist) LEDD=1353 mg/day at both baseline and at month 6, and the blinded UPDRS motor score in the on-medication/on-stimulation state changed from 41 at baseline to 30 at month 6; the other had baseline LEDD=2703 mg/day and month 6 LEDD=1289 mg/day, and the blinded UPDRS motor score in the on-medication/on-stimulation state changed from 18 at baseline to 17 at month 6.

Proxy symptoms of increased risk for suicide ideation and behaviours at 6 months

Examining the 19 psychological and psychiatric items from the PDQ-39 and SF-36 chosen as proxy symptoms of increased risk for suicide ideation and behaviours, there were three significant (and one trend) between-group differences in the DBS surgery versus BMT

controlled phase, all in favour of DBS surgery (table 2). Controlling for baseline response, patients randomised to DBS surgery were significantly more likely to report feeling full of life, happier and energetic, and less likely to feel tired and in pain, compared with BMT patients. There was a trend for DBS patients to feel more calm/peaceful compared with BMT patients.

Comparing STN with GPi surgery patients over this same 6-month period and controlling for baseline response, there were three significant between-group differences, all in favour of the GPi surgery group. Specifically, GPi patients were happier, less angry or bitter and less tired compared with STN patients.

Acute and chronic suicide ideation and behaviours in STN versus GPi patients

Rates of new-onset suicide ideation at 6 months were similar for patients randomised to STN versus GPi DBS (1.5% vs 0.7%) (table 3). Over the total 2-year follow-up period, for all DBS patients who provided follow-up data, two participants reported suicide behaviours, either a suicide attempt (n=1) or suicide completion (n=1). The suicide completion was in a patient randomised to GPi DBS, and the suicide attempt in a patient randomised to STN DBS. Of note, both patients had complicated medical-neurological courses postoperatively, as outlined in the case descriptions below.

Case summaries of DBS surgery patients with suicide behaviours

Case 1—A divorced research participant was originally randomised to BMT, then 3 months later was rerandomised to GPi STN. On the first night after DBS surgery, the patient had a left hemisphere cerebrovascular accident secondary to an intracranial haemorrhage lateral to the left DBS lead, with expressive aphasia and right-sided weakness. The patient remained hospitalised for 6 weeks and experienced some memory problems, word finding difficulties, depressive symptoms, and emotional lability, and was started on an antidepressant. From this point onward the patients lived either in a nursing home, assisted living, or other group setting. Approximately 1 month later, the cognitive and psychiatric symptoms had improved. Two months later, the patient became febrile, was diagnosed with pneumonia, and was hospitalised for several days and discharged in an improved state on antibiotics and short-term steroid treatment. Approximately 1 month later, the patient was seen for the 6-month study assessment, and the blinded UPDRS motor score in the on-medication/on-stimulation state changed from 24 at baseline to 29 at month 6, a worsening of five points (for comparison, the mean improvement for the DBS group in the medicated state at 6 months was 2.4 points¹⁵). In addition, the total LEDD changed from 1276 mg/day at baseline to 950 mg/day at month 6. At this visit, the patient expressed worsening depressive symptoms and suicide ideation, and was hospitalised psychiatrically at this time for approximately 1 month, had an adjustment to antidepressant medication in addition to receiving psychosocial treatment, and felt much improved on discharge. Approximately 4 months later (or 10 months postsurgery), the patient committed suicide (the patient was found by his caretaker with a bag over his head and a belt around his neck). The suicide was attributed to situational depression and overall physical decline, given the postoperative time course, self-reported financial hardships, extensive medical complications postoperatively

and stability of the DBS settings prior to the suicide. This event was listed as a completed suicide.

Case 2—A divorced research participant was originally randomised to BMT, then 6 months later was rerandomised to STN DBS. Approximately 4 months later the patient was admitted to a hospital with lower back pain and difficulty urinating, and was diagnosed with degenerative joint disease and spinal stenosis. At the month 6 study visit, the blinded UPDRS motor score in the on-medication/on-stimulation state changed from 33 at baseline to 38, a decline of five points (as mentioned previously, the mean improvement for the DBS group in the medicated state at 6 months was 2.4 points). In addition, the total LEDD was 675 mg/day at both baseline and at month 6. Around this time, the patient was admitted to the hospital with severe chest pain, and was diagnosed with chest pain secondary to cholelithiasis. Approximately 3 months later (or 9 months postsurgery), the patient, who was living alone, took a large amount of alprazolam tablets in a suicide attempt, was admitted to a psychiatric unit for 2 weeks, and received ongoing psychiatric treatment after discharge from the hospital. This event was listed as a suicide attempt.

DISCUSSION

The results from this randomised controlled trial suggest that suicide ideation and behaviours are not elevated in the 6-month period post-DBS surgery. In addition, psychological and psychiatric symptoms that might increase the risk for suicide behaviours are either similar or better in patients undergoing DBS surgery compared with those receiving ongoing medical therapy. Finally, there was no difference in suicide ideation or behaviours in STN versus GPi surgery patients followed out to 24 months, with events rare in both groups to this time point.

These findings are in contrast to case reporting and the results of retrospective studies,^{11–14} which have led to the belief that DBS surgery may directly lead to suicide behaviours. However, other research done to date have not evaluated patients in a systematic, prospective manner and have not included a control group of PD patients not undergoing DBS surgery. Combining outcomes from this study with the other two large randomised, controlled (DBS vs BMT) studies completed to date in advanced PD;^{22,23} there has been one completed suicide in 377 patients (0.27%) receiving DBS during the studies' controlled phases (duration 6–12 months). This suicide completion rate is one-third of the death rate in these studies secondary to DBS surgery-related acute cerebral haemorrhage (3/377 (0.80%) patients).

Our results suggest that DBS surgery itself does not increase the risk of suicide behaviours in PD beyond the already established risk factors in the general population (eg, medical complications and divorce) and those suggested from the general PD case literature (eg, younger age, history of major depression, previous suicide attempt and history of impulse control disorders (ICD)). This is in contrast to ICD disorder studies in PD, which suggest both non-specific (eg, younger age, family and personal history of ICDs) and PD-specific (ie, dopamine agonist treatment) risk factors for ICD development.²⁴

In the aforementioned retrospective case-control study,¹⁴ the decrease in total daily LEDD postsurgery was approximately 50–60%. In other recent open-label research in 63 PD patients that implemented a forced 75% reduction in total LEDD in the immediate aftermath of DBS surgery, patients overall experienced a significant increase in apathy, and two patients committed suicide within a 1-year period.²⁵ Thus, an acute, significant decrease in dopaminergic therapy postoperatively, as opposed to DBS surgery itself, may contribute to the development of suicide behaviours in a small subset of patients post-DBS surgery. In support of this hypothesis, during the controlled phase of the CSP 468 study, the DBS surgery group had a much smaller (approximately 25% on average) postoperative decrease in daily total LEDD.¹⁵ Although counterintuitive, it is possible that a modest, compared with robust, improvement in motor symptoms and a concomitant smaller decrease in dopaminergic therapy post-DBS surgery may help protect against development of suicide behaviours. Alternatively, GPi DBS compared to STN DBS might be protective against development of depression or suicide ideation/behaviours because it is comparable to STN DBS with respect to motor outcomes but does not require postoperative reduction of medications as is usually the case for STN DBS.

It is noteworthy that significant, protracted medical complications occurred soon after DBS surgery in both cases of suicide behaviours, which has been reported in other case series.²⁵ Medical problems are consistently reported to increase the risk of suicide ideation and behaviours,²⁶ so it is also possible that the medical and neurological complications of DBS surgery, not the surgery itself or actual electrical stimulation, is a risk factor for suicide behaviours that occur postsurgery. In addition, both patients were divorced, which is also a risk factor for suicide behaviours.²⁷

Much of the case literature for reporting suicide outcomes post-DBS surgery includes patients with significant psychiatric comorbidity prior to DBS surgery, including personality disorders, depression, bipolar disorder, previous suicide attempts, psychosis and ICDs.¹¹¹⁴²⁸²⁹ In this study, the two patients who reported new-onset suicide ideation in the controlled phase had baseline BDI scores that exceeded the recommended cut-off point for a diagnosis of depression. As psychiatric disorders are also risk factors for suicide in the general population, it is impossible to know without additional controlled research if there is an interaction effect between significant presurgical psychiatric disorders and DBS surgery that might lead to suicide behaviours postoperatively.

A limitation of the study was that there were a small number of dropouts by the 6-month evaluation, although there was no indication that any of the reasons listed for study discontinuation would be related to suicide ideation or behaviours. Given that women were more likely to drop out in the BMT group and increasing age was associated with discontinuation in the DBS surgery group, and female sex and younger age are risk factors for suicide attempts in the general population;⁵ the pattern of dropouts might have led to an underestimate of suicide ideation and attempts in the BMT group relative to the DBS surgery group. Another limitation was the use of the UPDRS depression item to document the presence of suicide ideation, as opposed to having available a separate, detailed assessment of death and suicide ideation. The UPDRS depression item has not been validated for the detection of suicide ideation, and raters administering this item were not

instructed to specifically ask about suicide ideation, so it is possible that we underestimated the frequency of suicide ideation in the study population. Although total BDI scores were available, scores for individual BDI items, including the suicide item, were not. Third, the controlled phase of the study lasted 6 months, but there is little reason to think that a specific DBS-related increased risk of suicide behaviours would not present itself in the 6-month period immediately after surgery, when the most significant medication and stimulator setting adjustments occur. Finally, although there was a control group in this study, there was not a sham surgery group to blind treatment assignment.

Over the years, case reporting, observational studies and retrospective studies have suggested an increased risk of suicide behaviours post-DBS surgery, leading to definitive statements such as DBS surgery being associated with ‘a striking increase in suicide rate in the first year postsurgery’³⁰ and ‘suicidal behaviour is a potential hazard of STN DBS’²⁸ but our findings from a prospective, randomised, controlled study found no increase in suicide ideation, suicide behaviours or related symptoms post-DBS surgery. Rather, accumulating data suggest that sudden, large decreases in dopaminergic medications, significant and protracted comorbid medical disorders, and major psychiatric comorbidity or other general risk factors for suicide may contribute to the development of suicide ideation and behaviours in PD patients in general.

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Figure 1.
Patient randomisation and dropouts during controlled phase.

Table 1

Incident suicide ideation and behaviours during controlled phase (DBS vs BMT)

	Baseline		3 Months		6 Months	
	(N=254) Suicide ideation*	(N=255) Suicide behaviours†	(N=224) Suicide ideation	(N=236) Suicide behaviours	(N=224) Suicide ideation	(N=232) Suicide behaviours
DBS	0 (0%)	–	0 (0%)	0 (0%)	2 (1.9%)	0 (0%)
BMT	0 (0%)	–	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)
p Value‡	n/a	–	n/a	n/a	0.61	n/a

* Based on UPDRS Part I depression item, the denominator is the total number of participants who had the complete data for this item.

† Based on adverse event reporting for time period since previous study visit, the denominator is the total number of participants who were at risk during the period.

‡ Fisher's Exact Test.

Table 2

Potential risk factors for suicide ideation and behaviour at 6 months

	DBS versus BMT: Phase I				DBS only: Phase II			
	DBS (N=106) (%)	BMT (N=116) (%)	p Value*	p Value [†]	STN (N=139) (%)	GPI (N=132) (%)	p Value*	p Value [†]
PDQ-39 items [‡]								
Worried about future	23.6	29.3	0.33	0.70	25.0	18.7	0.21	0.88 [§]
Felt depressed	11.3	15.5	0.36	0.25	15.2	10.1	0.21	0.32
Isolated/lonely	9.4	13.8	0.31	0.49	11.4	8.6	0.45	0.80 [§]
Weepy/tearful	13.2	7.8	0.18	0.24	13.6	7.9	0.13	0.30
Angry or bitter	6.6	4.3	0.45	0.19	12.1	2.9	0.004	0.001
Anxious	15.2	22.4	0.17	0.21	15.3	12.2	0.47	0.65
Dreams or hallucinations	6.6	12.1	0.16	0.18	12.1	8.0	0.26	0.41
Memory failing	21.7	21.6	0.98	0.83	22.0	23.0	0.84	0.87
SF-36 items								
Pain [¶]	41.5	51.7	0.13	0.05	44.3	42.8	0.80	0.66
Full of life**	43.4	23.5	0.002	0.009	33.6	40.3	0.25	0.43 [§]
Nervous**	6.6	13.8	0.08	0.19 [§]	9.2	5.8	0.29	0.29
Down in dumps**	1.9	4.3	0.30	0.31	1.5	2.2	0.69	0.51
Calm/peaceful**	57.6	44.0	0.04	0.06	46.6	54.0	0.22	0.76 [§]
Energy**	25.7	7.9	<0.001	0.001	18.2	24.1	0.24	0.33
Depressed**	7.6	8.6	0.77	0.71	6.8	5.8	0.72	0.91 [§]
Worn out**	20.8	25.2	0.43	0.63	25.8	18.7	0.16	0.27 [§]
Happy**	60.4	47.4	0.05	0.04	48.1	64.8	0.006	0.004
Tired**	29.3	40.5	0.08	0.03	35.1	23.7	0.04	0.03
Expect health to get worse ^{††}	41.5	50.0	0.20	0.27	45.5	39.1	0.29	0.36

* χ^2 test.[†] Cochran-Mantel-Haenszel test to adjust for baseline.[‡] Response 'always' or 'often'.[§] Variables having significant baseline difference between groups.[¶] Response 'very severe', 'severe', or 'moderate'.

** Response 'all of the time' or 'most of the time'.

^{††} Response 'definitely true' or 'mostly true'.

Table 3

Suicide ideation and behaviours in STN versus GPI patients

	Baseline		6 months		12 months		24 months	
	(N=298) Suicide ideation *	(N=299) Suicide behaviours [†]	(N=274) Suicide ideation	(N=279) Suicide behaviours	(N=258) Suicide ideation	(N=270) Suicide behaviours	(N=259) Suicide ideation	(N=261) Suicide behaviours
STN	0 (0%)	–	2 (1.5%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)
GPI	1 (0.7%)	–	1 (0.7%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)
p Value [‡]	1.0	–	0.61	n/a	n/a	1.0	n/a	n/a

* Based on UPDRS Part I depression item, the denominator is the total number of participants who had the complete data for this item.

[†] Based on adverse event reporting for time period since previous study visit, the denominator is the total number of participants who were at risk during the period.[‡] Fisher's Exact Test.