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Chapter 12

Psychiatric considerations in deep brain stimulation for Parkinson's disease

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INTRODUCTION

Parkinson's disease (PD) is a progressive neurological disorder with prominent nonmotor symptoms including psychiatric, cognitive, somatic, and autonomic disturbances. Deep brain stimulation (DBS) targeting the subthalamic nucleus (STN) or globus pallidus internus (GPi) is very effective for the symptomatic treatment of PD, improving both motor function and quality of life (Deuschl et al., 2006; Weaver et al., 2009). The assessment and management of psychiatric issues is relevant to preoperative selection of patients and to optimal postoperative outcomes, although evidence to guide clinicians is limited. An expert consensus and review published in 2011 summarized the role of psychiatric issues in DBS for PD (Bronstein et al., 2011). The review emphasized that, although surgery is usually deferred pending management of unstable psychiatric conditions, there was a lack of consensus on psychiatric symptoms as exclusion criteria. The review further highlighted the reported increased rate of suicide following STN DBS in patients with PD, emphasizing the necessity for careful preoperative and postoperative psychiatric assessment and follow-up, and management of depression. This chapter reviews the latest evidence for the role of psychiatric issues in DBS for PD.

PATHOPHYSIOLOGY

Postoperative psychiatric symptoms may be related to the following factors, some of which are interrelated or interactive: pre-existing psychiatric vulnerability, the neurobiology of PD, stimulation effects, medication changes, and psychosocial changes. For instance, pre-existing psychiatric vulnerability such as a history of depression (Okun et al., 2011) or ICDs (Voon et al., 2008) may contribute to higher postoperative depression scores or suicidal behaviors respectively. The neurobiology of PD, for example neurodegeneration affecting mesolimbic regions, is implicated in postoperative apathy, anxiety, and depression (Thobois et al., 2010). Postoperative decreases in dopaminergic medication dosages may also contribute to changes in mood and motivation (Thobois et al., 2010). Patients may also experience dopamine agonist withdrawal syndrome (DAWS) with behavioral symptoms of anxiety, panic, or dysphoria along with other nonmotor symptoms occurring with rapid withdrawal (Nirenberg, 2010). Patients with PD may also be more sensitive to DAWS (Rabinak and Nirenberg, 2010). Of note, nonmotor signs that are unmasked by decrease in dopaminergic medication may appear at an interval of several months (Thobois et al., 2010). Dopaminergic medications can also interact synergistically with stimulation to produce manic symptoms (Romito et al., 2002) or impulsive behaviors, such as binge-eating or hypersexuality (Lim et al., 2009). The decreases in dosage or withdrawal of dopamine agonists may therefore be useful particularly in the management of preoperative impulse control behaviors (Thobois et al., 2010). This effect may be related to the progressive desensitization of the psychotropic effects of dopaminergic medications (Castrioto et al., 2013). Like other major life-changing interventions, the postoperative state is also characterized by significant psychosocial changes including issues such as the patient's expectations

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for surgery, identity, work, and relationships (Houeto et al., 2006).

Stimulation may itself have an effect, with case reports of acute stimulation-induced behaviors of mania, disinhibition, depression, and aggression (Krack et al., 2010; Volkmann et al., 2010). Stimulation of the limbic-associative STN (below, anterior, and medial to the sensorimotor STN, which is the optimal motor target) has been associated with both positive and negative mood symptoms (Funkiewiez et al., 2003; Krack et al., 2010). The STN is a small nucleus (180 mm^3) (Yelnik, 2002) within the indirect pathway of the corticostriatal circuitry receiving input from the globus pallidus externa and output projections to the substantia nigra pars reticulata and globus pallidus interna, and also receives "hyperdirect" projections from cortical regions (Nambu et al., 2002; Haynes and Haber, 2013). Although the conceptualization of the corticostriatal circuitry is now increasingly complex, it is broadly divided into functional territories, which similarly are functionally subdivided in the STN (Yelnik, 2002). Given the small size of the nucleus, current spread is likely to affect the ventromedial cognitive and limbic regions (Krack et al., 2010).

SUICIDAL BEHAVIORS

Suicidal behaviors were reported to be increased in a retrospective international multicenter study involving over 5000 patients with PD who had undergone STN DBS (Voon et al., 2008). Completed suicides occurred in 0.45% (24 of 5311) and attempted suicides in 0.90% (48 of 5311). Relative to the general population (standardized mortality ratio for lowest and highest expected age-, sex-, and country-adjusted World Health Organization suicide rate 12.63–15.64), the standardized mortality rate from suicide in the first postoperative year (263 per 100 000 per year, 0.26%; $p < 0.001$) and remained increased in the fourth postoperative year (38 per 100 000 per year, 0.04%; $p < 0.05$) (Fig. 12.1). In the first postoperative year, suicide accounted for 13 excess deaths.

In the case–control arm of the study, completed suicides were associated with postoperative depression. Attempted suicides were associated with postoperative depression, being single, and a previous history of ICD, which accounted for 51% of the variance for attempted suicide risk. Attempted suicides were also associated with being younger, having younger onset of PD, and a previous suicide attempt. These results stand in marked contrast to the low rates of completed suicide in PD, which have been reported as being less than 10 times the general population. Furthermore, the mortality rate following surgery is reported as 0.4%, suggesting that postoperative suicide risk is potentially one of the most important and modifiable risk factors

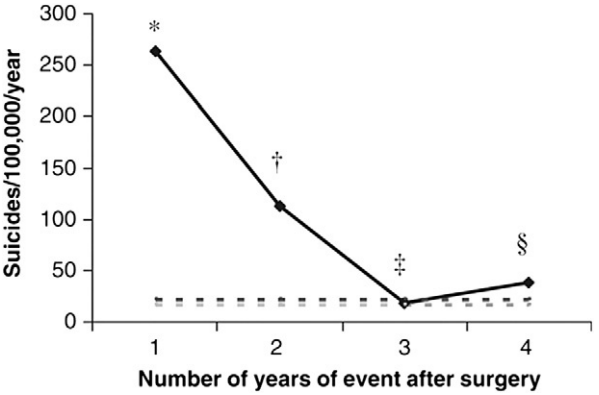

Fig. 12.1. Suicide rate per postoperative year following subthalamic nucleus (STN) deep brain stimulation (DBS) for advanced Parkinson's disease compared with baseline suicide rate. The observed postoperative STN DBS suicide rates per 100 000/year (solid line) and the lowest (grey dotted line) and highest (black dotted line) age-, sex-, and country-adjusted World Health Organization expected suicide rates per 100 000 per year are shown. $*p < 0.001$, $\dagger p < 0.001$, $\ddagger p > 0.05$, $\S p < 0.05$. (Adapted with permission from Voon et al., 2008.)

for postoperative mortality. It is not known whether the rate of suicide in typical candidates for surgery with advanced PD differs from this rate. The suicide rate in candidates presenting for surgery may also be biased.

Overall, patients should be assessed in a multidisciplinary manner and decisions for surgery made based on an individual basis considering a range of factors. Thus, no single psychiatric issue should be considered an exclusion criterion. For instance, a patient with a history of suicide attempt of low lethality in the distant past in the context of a depression with significant stressors may be at lower risk than a poorly compliant patient who is single without adequate supports, presenting with a severe ICD and borderline cognitive function, and who lives far away from adequate medical services. Based on clinical experience, other factors include unrealistic expectations, apathy, and prominent decreases in dopamine agonists. Patients should be prepared carefully for surgery, with closer postoperative follow-up for patients at risk and treatment of any postoperative anxiety, depression, or apathy. Patients should be referred to a psychiatrist if there are concerns surrounding suicide risk during the preoperative or postoperative assessment. Patients and family members should be on the lookout for suicidal ideation or postoperative depression, and active enquiries made during postoperative assessments. Patients may be experiencing DAWS with associated behavioral symptoms, necessitating an increase in the dopamine agonist dose (Nirenberg, 2010; Lhommée et al., 2012; Pondal et al., 2013; Thobois, 2013).

DEPRESSION

Depression is common, occurring in 30–40% of patients with PD (Reijnders et al., 2008), and is one of the most important predictors of quality of life in PD (Schrag, 2006). Postoperative depression is clinically relevant both as a correlate of postoperative quality-of-life outcomes (Zahodne et al., 2009; Daniels et al., 2011) and of postoperative suicidal behaviors (Voon et al., 2008). Past reviews have suggested that depression may occur in the early postoperative period, with individual case diagnoses reported in 20–25% of patients in the first few months (Voon et al., 2006). In a meta-analysis of studies, including those in which the focus was not on systematic psychiatric assessment, depression is reported in 2–4% (Appleby et al., 2007). Well designed prospective randomized controlled trials (RCTs) have since been conducted focusing on the issue of depression.

In a RCT of 60 PD pairs versus medical management, there were no differences in the group scores of the Montgomery Asberg Depression Rating Scale or Brief Psychiatric Rating Scale from baseline to 6 months (Deuschl et al., 2006; Witt et al., 2008). However, 4 of 60 patients (6.7%) developed a diagnosis of moderately severe depression following DBS, compared with 0 of 60 in the control group. A recent RCT compared STN DBS versus best medical treatment early on in the course of the disease. After a follow-up of two years, there was no deleterious effect of DBS on depression scores. On the contrary, there was a small but significant difference in favor of the DBS group compared to the arm on best medical treatment (Schuepbach et al., 2013). One patient committed suicide in the DBS group and 1 patient died in a car accident during a psychotic episode in the control group (Deuschl et al., 2006; Witt et al., 2008). In another multicenter RCT comparing STN (60 patients), GPi (61), and best medical therapy (134), no group differences were observed in the Beck Depression Inventory (BDI) score, although there were significantly more individual diagnoses of depression in the DBS group compared with medical management ($p = 0.03$) (Deuschl et al., 2006; Follett et al., 2010). Thus, overall, in well selected populations (i.e., no moderately severe depression at the time of preoperative assessment), individual cases of depression may be more likely to occur following DBS surgery irrespective of the target.

The relationship between depression and STN and GPi DBS has been delineated further. In a well designed RCT, depressive symptoms as measured after 2 years using the BDI worsened following bilateral STN surgery (147 patients: mean $\pm$ SD 11.2 $\pm$ 7.1 to 12.5 $\pm$ 8.5) and improved following bilateral GPi surgery (152 patients; 10.4 $\pm$ 7.8 to 9.8 $\pm$ 7.3) (difference: -1.9, (95% confidence interval -3.6 to -0.2), $p = 0.02$) (Follett et al., 2010). However, the change in score is very small. Moreover, in a long term follow-up there was one completed suicide in the GPi group and none in the STN group (Weintraub et al., 2013). The BDI has been validated in PD with recommended cutoff for screening at a score of 13/14 (Schrag et al., 2007). Whether the significant change in medication dosage (decrease in dopaminergic treatment in STN DBS but not in GPi DBS) might account for the mood differences is not known. Depression was diagnosed in 26.3% undergoing GPi versus 36.7% undergoing STN surgery ($p = 0.06$). Although much more work needs to be done, these findings suggest a potential role for selecting GPi target in those at high risk for the development of postoperative depression (Weaver et al., 2009).

Two prospective studies have addressed the question of whether patients with a preoperative history of depression are at greater risk of developing postoperative depression. In one, a personal history of depression, family psychiatric history, and preoperative depression scores did not differentiate those who developed postoperative depression (25%) from those who did not (Houeto et al., 2002). In a comparison of unilateral STN and GPi at 6 months in 110 patients, patients who were stable but with a preoperative history of depression had higher BDI scores (mean $\pm$ SD 8.97 $\pm$ 7.55 versus 5.92 $\pm$ 5.71, $p = 0.04$) and less improvement (11.6%) on the Unified Parkinson's Disease Rating Scale (UPDRS) (Okun et al., 2011). Thus, a preoperative history of depression does not appear to be linked to postoperative individual diagnoses of depression but may be associated with higher depression scores and less motor improvement.

Acute stimulation-induced behavioral symptoms are useful in demonstrating a link between the behavior and specific targets of stimulation. In a classic paper, a depressive state was induced by stimulating a contact within the substantia nigra pars reticulata (which is ventral to the subthalamic nucleus). Greater stimulation induced blood flow was also demonstrated in the left orbitofrontal cortex, globus pallidus, amygdala, anterior thalamus, and right parietal lobe (Bejjani et al., 1999). One study comparing unilateral STN DBS (22 patients) or GPi DBS (23) provides evidence demonstrating no differences between targets in mood changes as measured using the Visual Analog Mood Scale (VAMS) when using optimal settings. In a secondary analysis, when comparing all four DBS stimulation settings (3 mm below target, 3 mm above target, optimal target used for chronic stimulation and on stimulation) at 7 months, the ventral stimulation settings often worsened many VAMS items across both targets (more confused, less energetic, less happy, and more sad). The authors suggested a relationship between stimulation of both STN stimulation and GPi ventral targets and mood changes reported after surgery (Okun et al., 2009). Other studies have shown the opposite effect. For instance, acute STN

stimulation resulted in a positive improvement in mood (Funkiewiez et al., 2003; Mallet et al., 2007), as did bilateral STN stimulation 1 year after surgery using well positioned electrodes (Funkiewiez et al., 2003). In this study, 50 patients with PD completed the Addiction Research Center Inventory (ARCI), assessing subjective psychotropic effects in four conditions: off-drug/on-stimulation; off-drug/off-stimulation; on-drug/off-stimulation; and on-drug/on-stimulation. Both L-dopa and STN DBS improved all the ARCI subscales, indicating subjective feelings of wellbeing, euphoria, increase in motivation, and decrease in fatigue, anxiety, and tension. A suprathreshold dose of L-dopa was significantly more effective than STN DBS, using the same electrical parameters as for chronic stimulation, on four of the five ARCI subscales. The authors concluded that: (1) both STN DBS and L-dopa have synergistic acute beneficial psychotropic effects in PD; (2) the psychotropic effects of both treatments need to be considered in the long-term management of chronic STN DBS; and (3) the results indicate an involvement of the limbic STN in mood disorders of PD. Finally, another study carefully compared the effects of mood with acute stimulation of electrodes localized within the STN in two parkinsonian patients who experienced transient hypomanic states after surgery. During the experiment, STN acute stimulation again induced a hypomanic state caused only by stimulation through one contact localized in the anteromedial STN, whereas both this contact and the contact immediately dorsal, also located in the STN and used for chronic stimulation, improved the parkinsonian motor state (Mallet et al., 2007). These findings of high stimulation parameters using electrodes located within the STN inducing hypomanic or manic states are compatible with the systematic study in a large cohort reported by Funkiewiez et al. (2003), reporting a psychostimulant effect of bilateral STN DBS, whereas the findings of Okun et al. (2009), reporting more sadness in a target 3 mm below the STN motor target, are compatible with the case report published by Bejjani et al. (1999). These studies on acute mood effects of stimulation emphasize the importance of precise targeting and expertise in adjusting stimulation parameters for the post operative management of not only in motor symptoms, but also in mood.

In summary, compared with medical management, group scores on depression scales are similar. Major depression after DBS stimulation occurs in 6% (after 6 months) to 26.3–36.7% (after 2 years) of patients is more frequently diagnosed compared with rates following medical management, and may be more frequent in STN DBS compared with GPi DBS. This may be related to greater withdrawal of dopaminergic medication in STN versus GPi DBS, rather than being related specifically to target site. Furthermore, dopaminergic medication withdrawal may contribute to progressive desensitization (Krack et al., 1999; Castrioto et al., 2013). Postoperative depression is also consistent with the increased frequency of depression in the first postoperative year following any life-changing surgery, such as in solid-organ transplantation. Patients with a preoperative history of depression may have higher postoperative depression scores along with less improvement on the UPDRS. It should be emphasized that depression is commonly transient and usually treatable, highlighting that patients should be followed closely after surgery. The presence of a current moderate to severe depression during the presurgical assessment is a contraindication for surgery and the patient should be reassessed following management of the depression. The presence of risk factors for depression should not be considered an absolute contraindication for surgery. Rather, identifying risk factors will be useful in identifying those requiring closer follow-up or who may benefit from different interventions such as GPi surgery rather than STN, if indeed the preliminary findings are replicated.

Clinicians should have a high index of suspicion for depression, particularly in patients with a premorbid history of depression. Systematic assessment of mood when selecting patients, at the time of surgery, and during follow-up is mandatory. Several self-rated and clinician-rated questionnaires have been validated in PD with cutoff scores higher than that of the general population (Schrag et al., 2007). There are no RCTs of treatment of postoperative depression. The evidence presented here focuses on the management of PD depression. Increases in dopaminergic medication dose, and particularly dopamine agonist doses, given the known efficacy of pramipexole in PD depression, may be considered as first-line treatment if the context is that of postoperative withdrawal of dopamine replacement therapy (Barone et al., 2010). However, if the depression is not that of a "specific" comorbid depression in PD with prominent apathy but absence of guilty thoughts and self-blame, and absence of suicidal behavior (Even and Weintraub, 2012), idiopathic depression may be more likely and the use of antidepressant treatment is indicated. The use of dopamine agonists and of antidepressants is not mutually exclusive. Depending on the behavioral profile of the patient (presence of apathy favoring dopamine agonists, absence of ICD contraindicating dopamine agonists), a pragmatic approach might therefore consist of a combination of both antidepressant treatment and dopamine agonists. A recent double-blind RCT demonstrated efficacy of paroxetine and venlafaxine in major depression of PD (Richard et al., 2012). Tricyclic antidepressants such as nortriptyline and desipramine have been shown to be efficacious (Miyasaki et al., 2006). Psychotherapy or couple counseling should be considered, given the significant changes in identity and social interactions.

APATHY

Apathy is defined as decreased motivation with decreased initiative, interest, and emotion (Dujardin and Defebvre, 2012). Apathy is positively associated with correlation of activity in the right inferior frontal gyrus, right middle gyrus, right cuneus, and right anterior insula on [^{18}F]fluorodeoxyglucose positron emission tomography (PET) (Dujardin and Defebvre, 2012; Robert et al., 2012). In a review of 13 studies focusing on apathy following DBS, 11 studies found an increase in postoperative apathy whereas 2 found no change in apathy (Kirsch-Darrow et al., 2011). There were no differences in unilateral GPi and STN stimulation, or laterality. Medication dosage changes were not associated with apathy in several studies. In a recent study focusing on 63 patients with bilateral STN DBS, in which dopamine agonists were discontinued and the dopaminergic dosage was decreased markedly by 82%, apathy developed in 54% after a mean of 4.7 months (Thobois et al., 2010). The symptom was reversible in half of these with an increase in dopaminergic medication. Transient depression developed in 27% (17 of 63), of which 16 of the 17 cases were in the apathy group. Predictors of apathy were preoperative nonmotor fluctuations and anxiety during the L-dopa test, but not motor or cognitive status or the decrease in medication dose. [^{11}C]raclopride PET suggests that differences in the denervation of the mesolimbic system affecting the left orbitofrontal cortex, dorsolateral prefrontal cortex, thalamus, GPi, and bilateral anterior and posterior cingulate cortices are associated with apathy (Thobois et al., 2010). In 48 patients with PD undergoing either unilateral GPi or STN DBS followed for 2, 4, and 6 months after surgery, apathy increased linearly by 0.66 points every 2 months in the surgery group compared with controls. Adults aged less than 65 years had a steeper trajectory of apathy than older adults. The trajectory of apathy was not related to motor severity or changes, the DBS target, preoperative depression scores, or medication changes (Kirsch-Darrow et al., 2011).

Apathy following DBS surgery is related to preoperative nonmotor fluctuations, anxiety, younger age, and mesolimbic degeneration. There is no clear relationship with whether the target is GPi or STN, motor or cognitive status. Symptoms of apathy can also develop at a much later stage after surgery (Thobois et al., 2010). Withdrawal of dopaminergic medications may also play a role in progressive desensitization (Castrioto et al., 2013). Postoperative apathy however is not an inevitable fate, provided patients are well managed, as shown in a recent RCT comparing STN DBS to best medical treatment with a follow up of two years. Indeed, there was no significant difference in apathy scores between the two treatment groups (Schuepbach et al., 2013). There is a close relationship between our clinical definitions of postoperative apathy and depression which might reflect an overlap in the constructs in the postoperative state with similar neurochemical or neuroanatomical substrates. That the initial management of both is similar would again suggest an overlapping relationship.

Given the impact of apathy on quality of life and the frequent association with anxiety and depression, it is important to screen for appearance of apathy after surgery. This risk should be explained to the patient and caregiver before surgery along with the possibility of delayed appearance of apathy after 6–12 months (Thobois et al., 2010). In patients at risk, as for example those with nonmotor fluctuations, pre-existing apathy, major decrease in dopaminergic medications, and more specifically of dopamine agonists (Rabinak and Nirenberg, 2010; Pondal et al., 2013), systematic evaluation with specific tools should be used before and after surgery for early detection. Apathetic behaviour will most likely be recognized first by the patient's caregiver, so information and screening should include both the patient and the caregiver. Subjects at higher risk might include those with preoperative nonmotor fluctuations and anxiety. Major decreases in dopaminergic medications and especially dopamine agonists can induce apathy in the context of DAWS (Rabinak and Nirenberg, 2010). Management focuses on increasing the dose of dopaminergic medication and, possibly more specifically, of dopamine agonists, which may improve the symptom (Czernecki et al., 2005; Rabinak and Nirenberg, 2010; Lhommée et al., 2012; Pondal et al., 2013; Thobois et al., 2013). Other interventions should include assessment for underlying depression or impaired cognitive status which might necessitate a different management. Interventions should include changes in environment to increase stimulation, structuring daytime activities including access to day programs, and family education and support.

HYPOMANIA AND MANIA

The rate of postoperative hypomania was reported in a meta-analysis as 0.9–1.7% (Appleby et al., 2007). Hypomania has been reported prior to STN stimulation initiation, suggesting an effect of localized edema or a microlesion effect (Romito et al., 2002). However, there are convincing reports that stimulation of the STN can induce mania in a voltage-dependent manner (Krack et al., 2001; Mallet et al., 2007). Hypomania and mania have been associated with dopaminergic medications. Patients treated with L-dopa or STN stimulation perceive similar subjective improvements in euphoria, motivation, fatigue, anxiety, and tension, suggesting mechanistic overlaps (Funkiewiez et al., 2006). In a study of two patients with reproducible stimulation-induced mania, using an interactive brain atlas, the active contacts were localized to the

ventral contacts in the anteromedial STN (Mallet et al., 2007). The authors argued that, as the manic syndrome characterized by mood, behavior, cognitive, and motor changes was induced by specific contacts and not others, the STN may act to integrate emotional, cognitive, and motor function. Mania in the first few postoperative months following STN DBS is well recognized as a sequelae of high stimulation parameters interacting with dopaminergic medications. Either a decrease in stimulation parameters or a decrease in dopaminergic medication dosage can result in symptomatic improvement.

ANXIETY

Anxiety disorders are very common in PD, are likely related to the underlying neurobiology of PD, and can precede the onset of motor symptoms by up to 20 years (Shiba et al., 2000). Anxiety is also part of nonmotor fluctuations, being a prominent nonmotor feature of the off state that can disappear in the on state. In the on state, those with off state anxiety can typically experience on state euphoria (Lhommée et al., 2012). In a RCT comparing DBS with medical management, anxiety scores were significantly decreased following surgery, with a significant improvement in Beck Anxiety Inventory scores (difference of change 10.43, 95 per cent confidence interval 6.08 to 14.78, Cohen D = 0.8) with a large effect size (Witt et al., 2008). The clinical implications of this finding are not completely clear, given that anxiety scales commonly assess somatic symptoms. Improvement in nonmotor fluctuations with off period anxiety related to STN DBS is the most likely explanation (Lhommée et al., 2012). Generalized anxiety disorder was diagnosed retrospectively in 18 of 24 patients with PD following STN DBS surgery in which 17 patients had a preoperative history of anxiety, indicating hat postoperative anxiety is related to the disease or nonmotor fluctuations rather than stimulation *per se* (Houeto et al., 2002). Assessment of anxiety and nonmotor fluctuations is part of the mandatory baseline assessment and follow-up.

IMPULSE CONTROL DISORDERS

ICD behaviors are common in PD and occur in up to 13.6% of medicated patients (Weintraub et al., 2010). The behaviors include pathological gambling, hypersexuality, binge-eating, compulsive shopping, punding, and compulsive medication use. Although the behaviors are associated with dopaminergic medications and have certain features in common, there are many differences between them.

ICD behaviors have been reported to improve, remain unchanged, or worsen after surgery (Lim et al., 2009). *De novo* onset of ICDs has also been reported (Smeding et al., 2007). There is as yet no clear consensus regarding the role of DBS for preoperative ICD and compulsive medication use. In two retrospective case series, mixed ICD behaviors were reported primarily to remain unchanged or worsen following bilateral STN DBS, unilateral STN, or GPi DBS. For instance, in one of the retrospective bilateral STN and GPi DBS case series that included both ICDs and compulsive medication use, postoperative worsening of symptoms was associated with lack of preoperative recognition of the disorder and high dopaminergic medication dose (Lim et al., 2009). Of note, in this study the group with an improvement in compulsive medication use had a greater postoperative decrease in dopaminergic medication dose. There was a significant association between poor behavioral outcome and lack of preoperative recognition of the behavior, poor or moderate motor outcome, and higher postoperative dopamine agonist dose. In another retrospective unilateral STN DBS case series, only 2 of 7 subjects with preoperative ICD improved, with no clear relationship to medication dose (Moum et al., 2012). That there were no significant changes in medication dosage following the unilateral DBS may be an important limiting factor. Compulsive medication use in 5 patients persisted in the postoperative stage. In this same case series, 17 of 159 patients developed new-onset ICD behaviors, although the exact nature of these behaviors was not reported. In contrast, other small restrospective studies have suggested that ICD can resolve after STN DBS and could become a new indication for surgery in this target (Witjas et al., 2005; Ardouin et al., 2006), thus proposing an opposing view compared with the traditional position that any type of behavioral disorder should be considered a contraindication for surgery (Houeto et al., 2002). In favor of this change in paradigm, in a prospective study including 17 patients with preoperative ICDs treated with bilateral STN DBS, using systematic preoperative and postoperative evaluation of ICD and systematic discontinuation of dopamine agonists, all ICD behaviors ceased (Lhommée et al., 2012). In this study, however, preoperative overall appetitive behavior changed into an overall more apathetic mode of functioning, which might mitigate the beneficial effect on ICD (Lhommée et al., 2012). Thus, we emphasize that careful preoperative behavioral assessment and management of postoperative medications is crucial. In a second prospective trial of STN DBS there was also a significant improvement in dopamine dysregulation syndrome, impulse control disorders and in addiction to dopaminergic medication one year after surgery (Eusebio et al., 2013).

Postoperative ICD may be related to an interaction between stimulation and medication. In a retrospective case series of 7 patients with premorbid pathological

gambling, the behaviors improved over time, time-locked to the decrease in medication doses (Ardouin et al., 2006). In a cohort of patients with presurgical ICD, those who did not improve ("poor outcome group") were on very high doses of dopaminergic treatment (mean ± SD daily L-dopa equivalent dose 2745 ± 1328 mg, median 2250 mg, range 532–5323 mg), with half of the patients remaining on dopamine agonist treatment. Attempts to reduce medication in this group, even in patients with a good motor outcome, were usually met with resistance.

Overall, although ICDs can occur after surgery, the case reports suggest that their occurrence, particularly that of pathological gambling or compulsive shopping, is rare. The existing data suggest that, with careful preoperative and postoperative assessment and management, there is a role for STN DBS in the management of ICDs in patients in whom medication changes are ineffective or poorly tolerated. Transient postoperative worsening might occur early in the postoperative stage. STN DBS allows a greater decrease in dopaminergic medication dose relative to GPi DBS, and enables a discontinuation of the dopamine agonist. However, patients may be reluctant to decrease their dopaminergic medication. Furthermore, dopamine withdrawal symptoms may be delayed by several months, and greater apathy rather than appetitive functioning may be a necessary compromise. Postoperative follow-up should utilize validated screening scales. Patients with ICD may also be at greater risk of DAWS, requiring careful titration of medications (Nirenberg, 2010), and of postoperative suicidal behaviors (Voon et al., 2008).

CONCLUSION

A range of neuropsychiatric symptoms can occur following DBS for PD. Many of these symptoms are transient and manageable. A high index of suspicion and systematic preoperative screening using adequate scales to detect patients at risk, along with careful postoperative management, are warranted.

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