Effects of STN and GPi Deep Brain Stimulation on Impulse Control Disorders and Dopamine Dysregulation Syndrome

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Abstract

Objective: Impulse control disorders (ICDs) and dopamine dysregulation syndrome (DDS) are important behavioral problems that affect a subpopulation of patients with Parkinson’s disease (PD) and typically result in markedly diminished quality of life for patients and their caregivers. We aimed to investigate the effects of subthalamic nucleus (STN) and internal globus pallidus (GPI) deep brain stimulation (DBS) on ICD/DDS frequency and dopaminergic medication usage.

Methods: A retrospective chart review was performed on 159 individuals who underwent unilateral or bilateral PD DBS surgery in either STN or GPI. According to published criteria, pre- and post-operative records were reviewed to categorize patients both pre- and post-operatively as having ICD, DDS, both ICD and DDS, or neither ICD nor DDS. Group differences in patient demographics, clinical presentations, levodopa equivalent dose (LED), and change in diagnosis following unilateral/bilateral by brain target (STN or GPI DBS placement) were examined.

Results: 28 patients met diagnostic criteria for ICD or DDS pre- or post-operatively. ICD or DDS classification did not differ by GPI or STN target stimulation. There was no change in DDS diagnosis after unilateral or bilateral stimulation. For ICD, diagnosis resolved in 2 of 7 individuals after unilateral or bilateral DBS. Post-operative development of these syndromes was significant; 17 patients developed ICD diagnoses post-operatively with 2 patients with pre-operative ICD developing DDS post-operatively.

Conclusions: Unilateral or bilateral DBS did not significantly treat DDS or ICD in our sample, even though a few cases of ICD resolved post-operatively. Rather, our study provides preliminary evidence that DDS and ICD diagnoses may emerge following DBS surgery.

Introduction

Dopamine agonist therapy and sometimes even levodopa therapy for Parkinson’s disease (PD) may be associated with hypersexuality, pathological gambling, compulsive eating, compulsive shopping, and other ICDs [1]. In PD patients dopamine replacement therapy may also result in a pathological overusage of levodopa [2] and this condition has been termed the dopamine dysregulation syndrome (DDS) [3–5]. The effects of STN and/or GPI deep brain stimulation (DBS) on these issues remains largely unknown, however many groups have argued that DBS, particularly in the STN, may be beneficial for these syndromes by simply facilitating dopamine agonist and levodopa reduction [6,7].

Most patients undergoing DBS are selected based on the potential for improvement of motor symptoms as well as for...
Methods

Ethics Statement
The reported study utilized a University of Florida Institutional Review Board (UF IRB) previously approved database for PD (INFORM-PD). The compiled data had been collected prospectively on all patients seen at the University of Florida Center for Movement Disorders & Neurorestoration. Written informed consent was received from all participants. To facilitate the current study, a second UF IRB approved retrospective chart review was conducted for all patients with PD identified using the database.

Participants
An Institutional Review Board (IRB) approved retrospective chart review was performed on 159 patients who underwent unilateral or bilateral DBS surgery at the University of Florida Center for Movement Disorders & Neurorestoration between January 2002 and January 2010. All patients operated at the University of Florida underwent a complete in person evaluation with a neuropsychologist, a psychiatrist, a neurologist, and a neurosurgeon (M.S.O.). The thresholds for stimulation-induced benefit (motor score (UPDRS-III OFF MEDICATION, or UPDRS-III ON MEDICATION) (all p < 0.05). There was no significant difference between diagnostic subgroups according to pre-operative dopamine agonist usage (χ^2(6) = 6.51, ns), Hoehn and Yahr Staging OFF MEDICATION (χ^2(15) = 9.51, ns), or Hoehn and Yahr Staging ON MEDICATION (χ^2(12) = 3.94, ns). Regarding pre-operative levodopa equivalent dose (LED), there was similar LED usage between patients with ICD and DDS (Mean ± S.D.: ICD = 734.06 mg ± 388.32 mg, DDS = 1270.83 mg ± 743.76 mg; Z = -1.03, ns) with the one ICD/DDS patient demonstrating LED usage that doubled that of the other groups (ICD/DDS = 2250.00 mg). Of the 159 patients in the cohort, Group Consensus – Two raters (S.J.M. and N.L.) served as the primary chart reviewers. They were required to review and be experts on the diagnostic criteria for ICDs and DDS prior to initiating the review process. For the study data, if raters disagreed on a diagnosis, discrepancies were resolved by tertiary expert raters to achieve consensus before conducting final analyses.

DBS Implantation
The procedures were performed by a fellowship-trained neurosurgeon (K.D.F.). Multiple pass microelectrode mapping was conducted by a fellowship-trained neurologist/ electrophysiologist (M.S.O.). The thresholds for stimulation-induced benefit and side effects were determined intra-operatively using macrostimulation via the implanted DBS lead. Each lead was placed in the sensorimotor region of the desired target (STN or GPi). Pulse generators were surgically implanted one month after lead placement, and patients were typically evaluated for programming and medication adjustments monthly for the first six months, and then every 3–6 months thereafter. Patients underwent unilateral DBS initially and were offered the addition of a contralateral DBS implantation after 6–7 months of follow-up if clinically indicated.

Statistical Analyses
Patients were initially separated into those with unilateral DBS and those with bilateral DBS. In the preliminary analysis, patients were classified based on pre-operative diagnosis (i.e., ICDs, DDS, both DDS and ICDs, or no ICD or DDS). Diagnostic groups were compared on demographics and particularly gender, as it has been reported that men are predisposed to ICD and DDS [11,12]. For both unilateral and bilateral DBS patients, the pre-and post-operative diagnoses were compared to determine whether the stimulation target (STN or GPi) had a significant effect on the outcome, whether any new diagnosis of ICD or DDS developed post-operatively, or whether symptoms of ICD or DDS resolved post-operatively. Analyses used non-parametric statistics (Kruskall-Wallace, Chi-Square). Significance was based on alpha .05.

Results
Of 159 participants, 24 patients (15.1%) met the diagnostic criteria for ICD and 7 (4.4%) for DDS, either pre- or post-operatively. Pre-operatively, 11/159 patients (6.9%) met criteria for ICD and 7 (4.4%) for DDS, either pre- or post-operatively. Post-operatively, 11/159 patients (6.9%) met criteria for ICD and 7 (4.4%) for DDS, either pre- or post-operatively. Post-operatively, 11/159 patients (6.9%) met criteria for ICD and 7 (4.4%) for DDS, either pre- or post-operative.

Diagnostic Group Demographics and Medication Usage
Table 2 shows baseline demographics and characteristics for all cohort patients. Pre-operative diagnostic subgroups were similar in age of onset for PD symptoms, age at the time of surgery, and motor score (UPDRS-III OFF MEDICATION, or UPDRS-III ON MEDICATION) (all p > 0.05). There was no significant difference between diagnostic subgroups according to pre-operative dopamine agonist usage (χ^2(6) = 6.51, ns), Hoehn and Yahr Staging OFF MEDICATION (χ^2(15) = 9.51, ns), or Hoehn and Yahr Staging ON MEDICATION (χ^2(12) = 3.94, ns). Regarding pre-operative levodopa equivalent dose (LED), there was similar LED usage between patients with ICD and DDS (Mean ± S.D.: ICD = 734.06 mg ± 388.32 mg, DDS = 1270.83 mg ± 743.76 mg; Z = -1.03, ns) with the one ICD/DDS patient demonstrating LED usage that doubled that of the other groups (ICD/DDS = 2250.00 mg). Of the 159 patients in the cohort,
Table 1. Definitions of DDS, ICDs, and Punding.

### Dopamine Dysregulation Syndrome (Giovanni 2000)

|   | Definition                                                                                           |
|---|------------------------------------------------------------------------------------------------------|
| A | PD with documented levodopa responsiveness                                                           |
| B | Need for increasing doses of DRT in excess of those normally required to relieve Parkinsonian symptoms and signs |
| C | Pattern of pathological use: expressed need for increased DRT in the presence of excessive and significant dyskinesias despite being ‘on,’ drug hoarding or drug seeking behavior, unwillingness to reduce DRT, absence of painful dystonias |
| D | Impairment in social or occupational functioning: fights, violent behavior, loss of friends, absence from work, loss of job, legal difficulties, arguments or difficulties with family |
| E | Development of hypomanic, manic, or cyclothymic affective syndrome in relation to DRT                  |
| F | Development of a withdrawal state characterized by dysphoria, depression, irritability, and anxiety on reducing the level of DRT |
| G | Duration of disturbance of at least 6 months                                                          |

### Impulse Control Disorders

#### Hypersexuality (Voon 2006)

|   | Definition                                                                                           |
|---|------------------------------------------------------------------------------------------------------|
| A | The sexual thoughts/behaviors are excessive or an atypical change from baseline marked by 1 of the following: |
|   | 1. Maladaptive preoccupation with sexual thoughts                                                    |
|   | 2. Inappropriately or excessively requesting sex from spouse or partner                                |
|   | 3. Habitual promiscuity                                                                             |
|   | 4. Compulsive masturbation                                                                           |
|   | 5. Calls to telephone sex lines or viewing of pornography                                            |
|   | 6. Paraphilias                                                                                       |
| B | The behavior must have persisted for at least 1 month                                                 |
| C | The behavior causes 1 of the following:                                                              |
|   | 1. Marked distress                                                                                  |
|   | 2. Attempts to control thoughts or behavior that are unsuccessful or result in marked anxiety or distress |
|   | 3. Becomes time consuming                                                                             |
|   | 4. Significant interference with social or occupational functioning                                  |
| D | The behavior does not occur exclusively during periods of hypomania or mania                         |
| E | If all criteria except C are fulfilled, the disorder is subsyndromal                                  |

#### Gambling (DSM-IV)

|   | Definition                                                                                           |
|---|------------------------------------------------------------------------------------------------------|
| A | Persistent and recurrent maladaptive gambling behavior as indicated by 5 (or more) of the following: |
|   | 1. Preoccupation with gambling                                                                      |
|   | 2. Increasing amount of money wagered                                                               |
|   | 3. Repeated unsuccessful attempts to control                                                        |
|   | 4. Restlessness or irritability when cutting down                                                    |
|   | 5. Gambles to escape from problems or to relieve dysphoric mood                                      |
|   | 6. Chases losses                                                                                     |
|   | 7. Lies to others about gambling                                                                    |
|   | 8. Performs illegal acts to finance gambling                                                         |
|   | 9. Jeopardized relationships, work, or education                                                     |
|   | 10. Relies on others for money                                                                     |
| B | Does not occur exclusively during periods of hypomania or mania                                     |

#### Compulsive shopping (McElroy 1994)

|   | Definition                                                                                           |
|---|------------------------------------------------------------------------------------------------------|
| A | Maladaptive preoccupation with buying or shopping that is manifested as impulses or behaviors       |
|   | 1. Are experienced as irresistible, intrusive, and/or senseless                                     |
|   | 2. Result in frequent buying of more than can be afforded, of items that are not needed, or during longer periods of time than intended |
| B | Cause marked distress, are time-consuming, significantly interfere with social or occupational functioning, or result in financial problems |
| C | The behaviors do not occur exclusively during periods of hypomania or mania                          |
71.1% were male with all 5 pre-operative DDS patients were male. This gender difference, however, did not reach statistical significance ($\chi^2(3) = 3.33, ns$).

### DDS and DBS Stimulation

Table 3 shows pre- and post-operative diagnoses for each patient with pre-operative DDS. After unilateral DBS placement, all 5/5 patients (100%) still fulfilled the DDS diagnostic criteria. Comparison of the effects of STN vs. GPi stimulation on DDS showed no change in DDS diagnosis relative to site of stimulation or pre-operative vs. 6 months post-unilateral DBS medication consumption according to LED level (all $p > 0.05$).

Of the 5 unilateral patients, 4/5 later had bilateral DBS placement. After bilateral DBS placement in the patients with pre-operative DDS, the diagnosis did not change (4/4 maintained DDS).

### Table 2. Baseline Demographics and Characteristics for All Patients in the Cohort.

|                             | ICD       | DDS       | ICD and DDSNo ICD or DDS | Total              | Significance among subgroups |
|-----------------------------|-----------|-----------|--------------------------|--------------------|-----------------------------|
| Mean age of PD (symptom) onset | 44.20±7.40 | 45.00±1.00 | 40.00                   | 48.84±9.54         | 48.54±9.40                  | $F(3,141) = 0.82, p = 0.49$ |
| Mean age at time of surgery | 58.50±7.50 | 60.50±7.14 | 50.00                   | 61.61±8.86         | 61.39±8.77                  | $F(3,155) = 0.82, p = 0.49$ |
| Mean UPDRS-III OFF MEDICATION | 45.83±19.83 | 43.50±9.88 | 32.00                   | 42.24±12.10        | 42.35±12.34                 | $F(3,143) = 0.40, p = 0.75$ |
| Mean Hoehn and Yahr Staging OFF MEDICATION | 3.00 | 3.00 | 2.5    | 2.87               | 2.88±0.71              | $\chi^2(15) = 9.51$ |
| Mean UPDRS-III ON MEDICATION | 28.20±10.94 | 20.00±6.88 | 20.00                   | 23.57±9.11         | 23.61±9.09                  | $F(3,133) = 0.68, p = 0.56$ |
| Mean Hoehn and Yahr Staging ON MEDICATION | 2.10 | 2.13 | 2.0 | 2.34               | 2.32±0.44              | $\chi^2(12) = 3.94$ |
| Mean pre-operative levodopa equivalent dose (mg) | 734.06±388.32 | 1270.83±743.76 | 2250.00         | 877.11±510.88       | 888.80±522.32              | $F(3,141) = 3.13, p = 0.03$ |
| Pre-operative dopamine agonist usage | 4/6 | 0/4 | 1/1 | 81/148           | 86/159                | $\chi^2(6) = 6.51$ |
| Gender (M/F)               | 3/3 | 4/0 | 1/0 | 105/43              | 113/46                | $\chi^2(3) = 3.33$ |

MEDICATION: all PD medications.

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Medication change after bilateral DBS could not be determined due to limited information as one patient died in an unrelated motor vehicle accident and another died of congestive heart failure (2/4 had LED information: preoperative = 1456.22 mg ± 1122.53 mg, 6 m post-bilateral = 1175.00 mg ± 35.36 mg). For these patients, 2/4 had bilateral placement in the STN and 2/4 patients had bilateral placement in the GPi.

### ICD and DBS Stimulation

Table 4 shows pre- and post-operative diagnoses for each patient with pre-operative ICD. Of the 7 patients with pre-operative ICDs, 1 patient underwent bilateral simultaneous DBS implantation and 6 patients underwent unilateral implantation. 4/6 patients went on to receive bilateral DBS placement. After unilateral DBS placement, 1/6 patients (16.7%) no longer met diagnostic criteria for ICD (placed in STN). Despite the resolution of ICD post-operatively for one patient implanted in the STN, the comparison of the effect of STN vs. GPI stimulation on ICD diagnosis did not yield a significant difference between the two targets ($\chi^2(1) = 1.20$, ns), although notably the sample size was small. Among the 6 unilateral DBS patients with pre-operative ICD, there also was no significant difference in pre-operative vs. 4 months post-unilateral DBS dopamine agonist usage ($\chi^2(1) = 0.60$, ns).

After bilateral placement, 2/4 patients (50%) with sufficient follow-up did not meet the diagnostic criteria for ICD. One case resolved after unilateral DBS and remained asymptomatic after the second surgery. The second case resolved after the additional contralateral DBS. There was no significant difference in pre-operative vs. 4 months post-bilateral DBS dopamine agonist usage ($\chi^2(1) = 2.92$, ns). Among the 2 patients with resolved ICD, one had bilateral placement in the STN, and the other had bilateral placement in the GPI.

### DBS Stimulation and Unmasking of Diagnoses

Among patients with pre-operative ICD, 2/7 subjects developed DDS after DBS placement, as shown in Table 4. Both of these patients were stimulated in the STN. Post-operative DDS was not diagnosed in any patient in our cohort who did not have either pre-operative DDS or ICD.

For ICD, among all of the DBS surgical interventions evaluated (unilateral and bilateral), 17 patients developed ICD post-operatively. Unilateral DBS was associated with 11/17 newly diagnosed ICDs. Of these 11 patients, 5 went on to receive bilateral DBS and in 4/5 patients (80%), the ICD resolved after the addition of contralateral DBS therapy. Staged bilateral DBS was associated with 6 new diagnoses of ICD after the second side procedure that had not been present after unilateral DBS. For all patients with new ICD diagnoses, there was no significant change in pre-operative vs. 4 months post-unilateral DBS dopamine agonist usage, pre-operative vs. 4 months post-bilateral DBS dopamine agonist usage, pre-operative vs. 6 months post-unilateral DBS LED level, or pre-operative vs. 6 months post-bilateral DBS LED level (all $p$>0.05). Of the patients who developed ICD post-unilateral DBS, 7/11 had lead placement in GPI and 4/11 had placement in STN. Of the patients who developed ICD post-bilateral DBS, 4/6 had bilateral placement in the STN and 2/6 had placement in the Gpi.

### Discussion

Using the criteria described above, we identified a group of 11 individuals with pre-operative DDS, ICD, or both DDS and ICD. Patients in this study all had interdisciplinary pre-operative evaluations for DBS, and these evaluations included questions addressing the criteria for diagnosing behavioral disorders. It is important however to note that when interpreting the data from
this study, that the awareness of these behavioral issues evolved
over many years, and therefore the reported numbers could
represent an underestimate of these features.

The findings from this study suggest that unilateral or bilateral
DBS had no clear effect on DDS, even if medication reduction was
realized. Quantitating medication intake in DDS and ICD, however,
can be challenging as exact doses and intervals may not be precisely known. The reason for the lack of precision is that
inherent to these syndromes is the potential for taking multiple
extra doses of medication. Moreover, since our center performs
unilateral DBS frequently, results should be interpreted with
cautions, as bilateral DBS is associated with more medication
reduction, and in a larger sample size may have led to greater
improvement in these behavioral features.

GPi vs. STN stimulation targets had no appreciable differential
effect on DDS symptoms. In contrast to the negligible effect of
DBS on DDS symptoms, the effect of DBS on ICDs appeared
more promising. One of seven patients with ICDs prior to
surgery resolved their ICD after unilateral DBS placement and
remained without ICD after staged bilateral DBS. An additional
patient recovered from ICD after bilateral DBS. There was no
significant decrease in dopamine agonist usage after either
unilateral or bilateral DBS. This observation may be a result of
our small sample size, however our results suggest that
discontinuation of dopamine agonist usage was not completely responsible for ICD resolution. An important limitation of this study is that surgical target (STN vs. Gi DBS) was either
determined by enrollment in a study (NIH COMPARE trial), or
determined by interdisciplinary evaluation and expert discussion.
This evaluative process may have led to a bias of implanting one
target over another for various reasons including the potential for
medication reduction with STN DBS. Future studies will need to
include a randomized cohort.

DBS may have unmasked some behavioral issues for select
patients, or alternatively DBS may have precipitated these
behaviors. Prior to DBS surgery, 11 individuals had presentations
consistent with ICDs, DDS, or both ICDs and DDS. Though
often identified during the pre-operative assessment, the treatment
of ICD and DDS has not been established, and as such groups
performing DBS have not always specifically excluded these
patients from surgery, and have also not routinely employed
treatment programs. Data from this study would suggest it will be
important in the future to identify and to address these issues pre-
operatively if possible.

Interestingly, after either unilateral or bilateral DBS placement
2 patients displayed new diagnoses of DDS. Several patients who
had not previously met the full diagnostic criteria for ICD or DDS
met criteria for ICDs post-operatively. The emergence of post-
DBS issues is an interesting and important observation [19,20].
Potential explanations are that these behavioral issues were
present, but not appreciated during pre-operative neuropsycho-
logical and psychiatric evaluations, or alternatively that DBS
unmasked or precipitated the onset of these new symptoms.
Larger, prospective studies will be necessary to clarify whether
there is any causal relationship between DBS and the genesis or
unmasking of these behavioral disorders, as has been shown in
dopamine agonist use [1]. It should be considered that DBS may
unmask underlying behavioral features, but also that DBS may,
like medications, be capable of causing ICD or DDS. Another
limitation of this study was that there was not a standardized
approach to medication reduction post-DBS, and medication
reduction may impact the appearance of these behavioral issues.

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**Table 4. Did Unilateral and Bilateral DBS Lead Placement Impact the Pre-operative Diagnosis of ICD?**

| Patient | Pre-operative Diagnosis | Diagnosis after Unilateral DBS Placement* (Target) | Diagnosis after Bilateral DBS Placement* (Targets) |
|---------|-------------------------|--------------------------------------------------|--------------------------------------------------|
| 1       | ICD                     | **Increased impulsivity, sexual indiscretions, punding** | ICD and DDS (STN, STN) |
| 2       | ICD                     | Excessive gambling and spending                    | No ICD or DDS (GPi, GPi) |
| 3       | ICD                     | ICD (GPi)                                          | *** |
| 4       | ICD                     | Excessive chocolate cravings, hyperphagia          | Increased sweet cravings, hyperphagia |
| 5       | ICD                     | Excessive gambling with scratch-off lottery tickets | ICD (STN) *** |
| 6       | ICD                     | DDS (STN)                                          | DDS (STN, STN) |
| 7       | ICD and DDS             | Pathological gambling and shopping                 | Need for excessive DRT, excessive spending and gambling, excessive money spent on adult entertainment, cannot maintain finances |

*DBS unilateral or bilateral lead target(s) noted in parentheses.

**Patient had simultaneous bilateral DBS lead placement. No diagnostic assessment was possible for the patient after unilateral placement.

***Patient did not have bilateral DBS lead placement.

DRT; dopamine replacement therapy including levodopa and/or dopamine agonists.

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Clinicians have been recently interested in studying the effects of DBS on ICDs and/or DDS, especially since these entities have proven to be difficult to address pharmacologically [7,19,20,28–30]. Some studies suggest that DBS improves DDS, while others indicate that DBS has no effect [7]. To complicate matters, while some studies indicate that DBS may be an effective therapy for ICDs, others suggest that it promotes their development [19,20,28,29]. All of these previously published studies included only a handful of patients. Well-designed, prospective studies will be required to elucidate the true effects of stimulation in various basal ganglia targets and to determine whether DBS improves, unmasks existing, or precipitates new DDS or ICDs. We suspect, based on the current analysis, that the story is complex and will require a much larger sample size to adequately sort out.

In conclusion, our experience indicated that neither unilateral nor bilateral DBS in the STN or the GPi resulted in resolution of pre-operative dopamine dysregulation syndrome. DBS did, however, show a potential therapeutic effect in two patients with impulse control disorders. One important observation was that DBS appeared to unmask or alternatively precipitate ICDs in some patients. It will be important in future studies to address the mechanisms that may underpin DBS precipitating these disorders. It will need to be determined whether direct limbic stimulation, or alternatively DBS is providing a second hit to a vulnerable genetic background or other process. Screening paradigms for DBS may need to be enhanced to include impulsivity, gambling, and other behavioral measures. Finally, family and spousal input seem to be important in uncovering at risk individuals. Careful prospective screening for these disorders and larger, prospective multi-center studies will be necessary to clarify the effects of DBS on DDS and ICDs. This research should address both therapeutic and potentially deleterious effects of DBS on these disorders.

Based on currently available evidence, clinicians should not consider unilateral or bilateral STN or GPi DBS to be a solution to Parkinsonian ICDs or DDS. Rather, heightened sensitivity to the significant prevalence and profound impact of these Parkinson-related behavioral disorders is warranted along with a more comprehensive approach to pre- and post-operative care. Patients should be carefully screened for ICDs and DDS before and after surgery to assess the true impact of DBS on these disorders. A thoughtful, patient-tailored treatment strategy for ICDs and DDS may also include judicious reduction of dopaminergic medications and behavioral therapies.

Author Contributions
Conceived and designed the experiments: MO KF SM. Performed the experiments: SM NL GO HW MO. Analyzed the data: CP SM MO KF. Contributed reagents/materials/analysis tools: CJ. Wrote the paper: SM MO CP KF NL GO HW CJ.

References
1. Voon V, Sohr M, Lang AE, Potenza MN, Siderowf AD, et al. (2011) Impulse control disorders in parkinson disease: A multicenter case-control study. Annals of Neurology 69: 906–909.
2. Giovannoni G, O'Sullivan J, Turner K, Manson A, Lees A (2000) Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. Journal of Neurology, Neurosurgery & Psychiatry 68: 423–428.
3. Pribe S (1984) Levodopa dependence: a case report. Psychopharmacology 17: 109–110.
4. Evans AH, Katzenschlager R, Paviour D, O'Sullivan JD, Appel S, et al. (2005) Pandling in Parkinson's disease: its relation to the dopamine dysregulation syndrome. Movement disorders 19: 397–405.
5. Nausieda PA (1985) Sinemet “abusers.” Clinical Neuropharmacology 8: 310–327.
6. Demetriades P, Rickards H, Cavanna AE (2011) Impulse control disorders following deep brain stimulation of the subthalamic nucleus in Parkinson's disease: clinical aspects. Parkinsons Dis, In press.
7. Knobel D, Aybek S, Pollo C, Vingerhoets FJ, Berney A (2008) Rapid resolution of dopamine dysregulation syndrome (DDS) after subthalamic DBS for Parkinson disease (PD): a case report. Cognitive and Behavioral Neurology 21: 187–190.
8. Chaudhuri KR, Martinez-Martín P, Schapira AH, Stocchi F, Sethi K, et al. (2006) International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. Movement Disorders 21: 916–923.
9. Martinez-Martin P, Schapira AH, Stocchi F, Sethi K, Odin P, et al. (2007) Prevalence of nonmotor symptoms in Parkinson’s disease in an international setting; study using nonmotor symptoms questionnaire in 545 patients. Movement Disorders 22: 1623–1629.

10. Nazzaro JM, Pahwa R, Lyons KE (2011) The impact of bilateral subthalamic stimulation on non-motor symptoms of Parkinson’s disease. Parkinsonism Relat Disord. In press.

11. Weintraub D, Koeter J, Potenza MN, Siderowf AD, Stacy M, et al. (2010) Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol 67: 589–595.

12. Cabrini S, Baratti M, Bonfà F, Cabri G, Uber E, et al. (2009) Preliminary evaluation of the DDS-PC inventory: a new tool to assess impulsive-compulsive behaviours associated to dopamine replacement therapy in Parkinson’s disease. Neurol Sci. In press.

13. Oken MS, Foote KD (2010) Parkinson’s disease DBS: what, when, who and why? The time has come to tailor DBS targets. Expert Review of Neurotherapeutics 10: 1047–1057.

14. Voon V, Hassan K, Ziworski M, de Souza M, Thomas T, et al. (2006) Prevalence of repetitive and reward-seeking behaviors in Parkinson disease. Neurology 67: 1254–1257.

15. Voon V, Fermaugut PO, Wickens J, Baunez G, Rodriguez M, et al. (2009) Chronic dopaminergic stimulation in Parkinson’s disease: from dyskinesias to impulse control disorders. Lancet 374: 1140–1149.

16. McElroy SL, Keck PE, Pope HG, Smith JM, Strakowski SM (1994) Compulsive buying: a report of 20 cases. Journal of Clinical Psychiatry 55: 242–248.

17. Nierenberg MJ, Waters C (2006) Compulsive eating and weight gain related to dopamine agonist use. Movement disorders 21: 524–529.

18. Friedman JH (1994) Punding on levodopa. Biological Psychiatry 36: 350–351.

19. Smeding HM, Goudriaan AE, Foncke EM, Schuurman PR, Speelman JD, et al. (2007) Pathological gambling after bilateral subthalamic nucleus stimulation in Parkinson disease. J Neurol Neurosurg Psychiatry 78: 517–519.

20. Halbich TD, Tse W, Frisina PG, Baker BR, Hollander E, et al. (2009) Subthalamic deep brain stimulation and impulse control in Parkinson’s disease. European Journal of Neurology 16: 493–497.

21. Avila A, Cardona X, Martin-Baranera M, Bello J, Sastre F (2011) Impulsive and compulsive behaviors in Parkinson’s disease: A one-year follow-up study. J Neurol Sci, In press.

22. Oei TP, Raylu N, Casey LM (2010) Effectiveness of group and individual formats of a combined motivational interviewing and cognitive behavioral treatment program for problem gambling: a randomized controlled trial. Behav Cogn Psychother 38: 233–238.

23. Rotondo A, Bosco D, Plastino M, Consoli A, Bosco F (2010) Clozapine for medication-related pathological gambling in Parkinson disease. Movement disorders 25: 1994–1995.

24. Stein DJ, Grant JE (2005) Betting on dopamine. CNS Spectrums 10: 268–270.

25. Koran LM, Bullock KD, Hartston HJ, Elliott MA, D’Andreia V (2002) Citalopram treatment of compulsive shopping: an open-label study. J Clin Psychiatry 63: 704–708.

26. Pallanti S, Quercioli L, Sood E, Hollander E (2002) Lithium and valproate treatment of pathological gambling: a randomized single-blind study. Journal of Clinical Psychiatry 63: 559–564.

27. Hicks CW, Pandya MM, Im I, Fernandez HH (2011) Valproate for the treatment of medication-induced impulse-control disorders in three patients with Parkinson’s disease. Parkinsonism & Related Disorders 17: 379–381.

28. Ardouin C, Voon V, Wurbe Y, Abouazzar N, Czernicki V, et al. (2006) Pathological gambling in Parkinson’s disease improves on chronic subthalamic nucleus stimulation. Movement disorders 21: 1941–1946.

29. Bandini F, Primavera A, Pizzorno M, Coccio L (2006) Using STN DBS and medication reduction as a strategy to treat pathological gambling in Parkinson’s disease. Parkinsonism & Related Disorders 13: 369–371.

30. Witjas T, Baumez C, Henry JM, Delfini M, Regis J, et al. (2005) Addiction in Parkinson’s disease: impact of subthalamic nucleus deep brain stimulation. Movement disorders 20: 1052–1055.