Dopamine Agonist Withdrawal Syndrome in Parkinson Disease

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Objectives: To report and characterize a dopamine agonist (DA) withdrawal syndrome (DAWS) in Parkinson disease.

Design: Retrospective cohort study.

Setting: Outpatient tertiary movement disorders clinic.

Patients: A cohort of 93 nondemented patients with Parkinson disease enrolled in a prospective study of nonmotor and motor disease manifestations.

Main Outcome Measure: The presence of DAWS, defined as a severe, stereotyped cluster of physical and psychological symptoms that correlate with DA withdrawal in a dose-dependent manner, cause clinically significant distress or social/occupational dysfunction, are refractory to levodopa and other Parkinson disease medications, and cannot be accounted for by other clinical factors.

Results: Of 40 subjects treated with a DA, 26 underwent subsequent DA taper. Of these 26 subjects, 5 (19%) developed DAWS and 21 (81%) did not. All subjects with DAWS had baseline DA-related impulse control disorders. Symptoms of DAWS resembled those of other drug withdrawal syndromes and included anxiety, panic attacks, agoraphobia, depression, dysphoria, diaphoresis, fatigue, pain, orthostatic hypotension, and drug cravings. Subjects with DAWS as compared with those without DAWS had higher baseline DA use (mean [SD], 420 [170] vs 230 [180] DA levodopa equivalent daily doses [DA-LEDD], respectively; *P = .04) and higher cumulative DA exposure (mean [SD], 1800 [1200] vs 700 [900] DA-LEDD-years, respectively; *P = .03). Subjects with DAWS also had considerably lower Unified Parkinson’s Disease Rating Scale motor scores than those without DAWS (mean [SD], 21 [5] vs 31 [10], respectively; *P = .007), despite comparable disease duration (mean [SD], 7.3 [7] vs 6.3 [4] years, respectively; *P = .77) and similar total dopaminergic medication use (mean [SD], 830 [450] vs 640 [610] total LEDD, respectively; *P = .52) in the 2 groups.

Conclusions: Dopamine agonists have a stereotyped withdrawal syndrome that can lead to profound disability in a subset of patients. Physicians should monitor patients closely when tapering these medications.

Arch Neurol. 2010;67(1):58-63

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DRUGS THAT INCREASE MESOCORTICOLIMBIC DOPAMINE, such as cocaine and amphetamines, produce physical and psychological dependence (addiction) and stereotyped withdrawal syndromes after prolonged, heavy use. Withdrawal syndromes are substance specific and commonly include anxiety, panic attacks, dysphoria, irritability, agitation, pain, sleep disturbance, fatigue, orthostatic hypotension, diaphoresis, and drug cravings. These symptoms cause significant distress or impairment in social/occupational functioning and can lead to suicidality.1

In Parkinson disease (PD), dopamine replacement therapy (DRT) is used to alleviate many of the disabling motor manifestations of the disease. These medications are adjusted to control motor symptoms attributable to nigrostriatal dopamine deficiency2 but also activate relatively intact mesocorticolimbic dopaminergic neurons.3,4 Thus, it might be expected that DRT—like other drugs that stimulate dopaminergic reward pathways—would also produce addiction and withdrawal.

Cases of DRT addiction, in which patients develop a maladaptive pattern of medication use and drug withdrawal symptoms reminiscent of a substance abuse disorder, have been well documented in PD. This phenomenon, referred to as dopamine dysregulation syndrome, is mainly associated with potent medications with short half-lives such as levodopa.5-10 More recently, dopamine agonists (DAs) have been shown to produce behavioral addictions, with an estimated 14% to 17% combined prevalence of impulse control disorders (ICDs) such as pathological gambling, com-
The concept of a withdrawal syndrome from DRT in PD is more complex because these medications are being used to treat a medical condition, and thus adverse neuropsychiatric symptoms are an expected consequence of drug withdrawal. The major difference is that symptoms attributable to undermedication or wearing off should respond to appropriate treatment with another form of DRT. In contrast, a drug-specific withdrawal syndrome would persist even with comparable (or higher) doses of other dopaminergic medications.

During a prospective cohort study of nonmotor and motor symptoms in PD, we identified several patients who developed severe nonmotor symptoms during tapering of DA. These symptoms responded only to DAs and not to levodopa or other medications, consistent with a DA withdrawal syndrome (DAWS). The goals of our study were to report and characterize DAWS and test the following hypotheses: (1) DAWS will selectively occur in subjects with DA addiction (ICDs); (2) the symptoms of DAWS will resemble those of other psychostimulant withdrawal syndromes; and (3) the risk of DAWS will be proportional to cumulative DA exposure.

## METHODS

A convenience sample of nondemented outpatients with PD (N=93) was recruited by one of us (M.J.N.) at a tertiary academic movement disorders center as part of a longitudinal study of nonmotor and motor manifestations of PD. Inclusion criteria included PD by the UK Parkinson’s Disease Society Brain Bank criteria,14 ability to provide informed consent, and ability to complete the research questionnaires. Exclusion criteria included a clinical diagnosis of dementia, modified Mini-Mental State Examination score lower than 25, dopamine receptor-blocking agent use, neurodegenerative disease other than PD, prior PD neurosurgery, or life expectancy of less than 12 months. The study was performed in accordance with the Weill Cornell Institutional Review Board.

A movement disorders specialist (M.J.N.) completed standard motor ratings, including the Unified Parkinson’s Disease Rating Scale (UPDRS) score and the modified Hoehn and Yahr stage. Subjects then underwent neuropsychiatric testing, including the Beck Anxiety Inventory, Beck Depression Inventory II, and Mini-Mental State Examination. Clinical assessments and record reviews were repeated annually. We diagnosed ICDs clinically based on consensus of the patient, caregiver, and treating physician. Data were entered into an electronic database (Microsoft Access; Microsoft Corp, Redmond, Washington). Levodopa equivalent daily doses (LEDD) were calculated as the following sum: regular levodopa + 0.375 times the dose of continuous-release levodopa + 1.3 times the dose of entacapone + 100 times the dose of pramipexole dihydropchloride or pergolide mesylate + 30 times the dose of rotigotine + 20 times the dose of ropinirole hydrochloride.23 Dopamine agonist LLED was defined as the LLED for DAs only. Cumulative DA exposure was approximated by multiplying the maintenance dose of DA (in LLED) by the duration of therapy.

Systematic record reviews were completed to identify all cases of DAWS, defined as a severe, stereotyped cluster of physical and psychological symptoms that correlate with DA withdrawal in a dose-dependent manner, cause clinically significant distress or social/occupational dysfunction, are refractory to levodopa and other PD medications (and thus occur even in the on state), and cannot be accounted for by other clinical factors. Subjects with DAWS were then compared with subjects in the cohort who underwent uneventful DA withdrawal (non-DAWS group). Statistical analysis was performed using GraphPad Instat version 3.0b for Macintosh (GraphPad Software, San Diego, California). We used t tests, Mann-Whitney U tests, and Fisher exact tests for parametric data, nonparametric data, and nominal variables, respectively. Statistical significance was defined as P < .05.

Of 93 subjects in the cohort, 40 (43%) had been treated with a DA and 26 (28%) had a DA tapered during routine patient care (Figure). The most common reason for DA taper was the presence of an ICD, which occurred in 15 subjects in the cohort (38% of all subjects who were treated with a DA, and 58% of those in whom a DA was tapered). Other reasons for DA taper included hypersomnia, psychosis, confusion, cognitive impairment, dizziness, orthostatic hypotension, and peripheral edema. Eventually, 13 subjects had the DA discontinued and 13 had the dosage of DA reduced, all with compensatory increases in levodopa dosage. Of the 26 subjects who had a DA tapered, 5 (19%) developed DAWS, with symptoms that included anxiety, panic attacks, depression, dysphoria, agitation, insomnia, dizziness, nausea, irritability, fatigue, orthostatic hypotension, diaphoresis, generalized pain, and drug cravings. In all cases, the onset of these symptoms correlated with initiation of the DA taper, and the severity of symptoms increased with incremental dose reductions. The symptoms were unresponsive to levodopa supplementation or adjustments to alleviate possible end-of-dose wearing off, persisting even when subjects were in the on state and/or markedly overmedicated. An additional subject with a history of ICDs had mild, transient anxiety and dysphoria at the time of DA taper, but this was self-limited and did not fulfill DAWS criteria.

Symptoms of DAWS were refractory to antidepressants, benzodiazepines, and cognitive behavioral therapy in subjects who received these treatments. In contrast, they rapidly and dramatically improved with DA repletion. No subjects with DAWS had a history of dopamine dysregu-
Table 1. Baseline Demographic and Clinical Features of Subjects With Dopamine Agonist Withdrawal Syndrome

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Age at PD Onset, y</th>
<th>Baseline UPDRS Motor Score</th>
<th>Baseline Modified Hoehn and Yahr Stage</th>
<th>ICDs or Punding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/67</td>
<td>60</td>
<td>26</td>
<td>2</td>
<td>Hypersexuality, buying, eating, sorting pills</td>
</tr>
<tr>
<td>2/F/61</td>
<td>55</td>
<td>15</td>
<td>1</td>
<td>Eating, buying, cleaning, painting, organizing</td>
</tr>
<tr>
<td>3/F/64</td>
<td>45</td>
<td>22</td>
<td>2.5</td>
<td>Eating, sorting pills</td>
</tr>
<tr>
<td>4/M/69</td>
<td>65</td>
<td>22</td>
<td>2.5</td>
<td>Hypersexuality</td>
</tr>
<tr>
<td>5/M/57</td>
<td>57</td>
<td>17</td>
<td>1</td>
<td>Hypersexuality, shopping, eating, gambling, praying</td>
</tr>
</tbody>
</table>

Abbreviations: ICDs, impulse control disorders; PD, Parkinson disease; UPDRS, Unified Parkinson’s Disease Rating Scale.

Motor assessments were completed when subjects were in the on state.

Table 2. Dopamine Agonist Exposure and Long-term Outcome of Subjects With Dopamine Agonist Withdrawal Syndrome

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Maximum DA-LEDD</th>
<th>Duration of DA Use, y</th>
<th>Cumulative DA Exposure, DA-LEDD-Years</th>
<th>Final DA-LEDD</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>500</td>
<td>6.5</td>
<td>3250</td>
<td>50</td>
<td>Chronic ICDs</td>
</tr>
<tr>
<td>2</td>
<td>450</td>
<td>5.1</td>
<td>2288</td>
<td>25</td>
<td>Chronic ICDs</td>
</tr>
<tr>
<td>3</td>
<td>600</td>
<td>3.5</td>
<td>2100</td>
<td>500</td>
<td>Chronic ICDs</td>
</tr>
<tr>
<td>4</td>
<td>400</td>
<td>3.0</td>
<td>1200</td>
<td>0</td>
<td>Recovery</td>
</tr>
<tr>
<td>5</td>
<td>150</td>
<td>0.5</td>
<td>75</td>
<td>0</td>
<td>Recovery</td>
</tr>
</tbody>
</table>

Abbreviations: DA, dopamine agonist; ICDs, impulse control disorders; LEDD, levodopa equivalent daily dose.

Table 3. Baseline Characteristics of Subjects With and Without Dopamine Agonist Withdrawal Syndrome, Just Prior to Dopamine Agonist Taper

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Subjects With DAWS (n=5)</th>
<th>Subjects Without DAWS (n=21)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>64 (5)</td>
<td>66 (9)</td>
<td>.56</td>
</tr>
<tr>
<td>Age at PD onset, y</td>
<td>56 (7)</td>
<td>58 (10)</td>
<td>.75</td>
</tr>
<tr>
<td>Disease duration, mean (SD), y</td>
<td>7.3 (7)</td>
<td>6.3 (4)</td>
<td>.77</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>3 (60)</td>
<td>8 (38)</td>
<td>.62</td>
</tr>
<tr>
<td>MMSE score, median (IQR)</td>
<td>30 (28-30)</td>
<td>29 (29-30)</td>
<td>.95</td>
</tr>
<tr>
<td>Smoking history, No. (%)</td>
<td>3 (60)</td>
<td>9 (43)</td>
<td>.63</td>
</tr>
<tr>
<td>UPDRS motor score, mean (SD)</td>
<td>21 (5)</td>
<td>31 (10)</td>
<td>.007</td>
</tr>
<tr>
<td>Pramipexole dihydrochloride use, No. (%)</td>
<td>5 (100)</td>
<td>15 (71)</td>
<td>.30</td>
</tr>
<tr>
<td>Total LEDD, mean (SD)</td>
<td>830 (450)</td>
<td>640 (610)</td>
<td>.52</td>
</tr>
<tr>
<td>DA-LEDD, mean (SD)</td>
<td>420 (170)</td>
<td>230 (180)</td>
<td>.04</td>
</tr>
<tr>
<td>Duration of DA use, mean (SD), y</td>
<td>3.7 (2)</td>
<td>2.8 (2)</td>
<td>.41</td>
</tr>
<tr>
<td>Cumulative DA exposure, mean (SD), DA-LEDD-years</td>
<td>1800 (1200)</td>
<td>700 (900)</td>
<td>.03</td>
</tr>
<tr>
<td>ICDs, No. (%)</td>
<td>5 (100)</td>
<td>10 (48)</td>
<td>.05</td>
</tr>
<tr>
<td>Anxiety, No. (%)</td>
<td>4 (80)</td>
<td>8 (38)</td>
<td>.15</td>
</tr>
</tbody>
</table>

Abbreviations: DA, dopamine agonist; DAWS, DA withdrawal syndrome; ICDs, impulse control disorders; IQR, interquartile range; LEDD, levodopa equivalent daily dose; MMSE, Mini-Mental State Examination; PD, Parkinson disease; UPDRS, Unified Parkinson’s Disease Rating Scale.

*Subjects who underwent DA taper without experiencing DAWS.

Collectively, subjects with ICDs (both with and without DAWS) had lower UPDRS motor scores than subjects without ICDs (mean [SD], 24 [8] vs 35 [9], respectively; P = .003), even though the 2 groups were similar with respect to both disease duration (mean [SD], 6.7

morbid history of anxiety in 4 (80%), depression in 2 (40%), prior smoking in 3 (60%), prior heavy alcohol use in 1 (20%), prior recreational gambling in 1 (20%), and marijuana use in 2 (40%). There was a family history of parkinsonism in 2 (40%) and drug abuse in 1 (20%); none reported a family history of anxiety, depression, alcoholism, or other ICDs. The severity of DAWS and long-term outcome correlated with DA exposure, with profound social/occupational dysfunction occurring in the 3 subjects with the greatest cumulative DA use; these subjects (patients 1-3) have been unable to discontinue DA and therefore experience chronic ICDs (Table 2).

Subjects with and without DAWS were similar with regard to age, age at PD onset, disease duration, sex, Mini-Mental State Examination scores, smoking history, pramipexole use, and total LEDD (Table 3). However, subjects with DAWS as compared with those without DAWS had significantly lower baseline UPDRS motor scores (mean [SD], 21 [5] vs 31 [10], respectively; P = .007), higher baseline DA doses (mean [SD], 420 [170] vs 230 [180] DA-LEDD, respectively; P = .04), and greater cumulative DA exposure (mean [SD], 1800 [1200] vs 700 [900] DA-LEDD-years, respectively; P = .03). Subjects with DAWS as compared with those without DAWS showed a trend toward a greater baseline prevalence of anxiety disorders (4 subjects [80%] vs 8 subjects [38%], respectively; P = .15) as well as a greater prevalence of restless legs syndrome after DA taper (3 subjects [60%] vs 4 subjects [19%], respectively; P = .10).

Collectively, subjects with ICDs (both with and without DAWS) had lower UPDRS motor scores than subjects without ICDs (mean [SD], 24 [8] vs 35 [9], respectively; P = .003), even though the 2 groups were similar with respect to both disease duration (mean [SD], 6.7
PATIENT 1

A 67-year-old, right-handed woman with a 6-year history of PD presented with predominantly right-sided rest tremor, rigidity, and bradykinesia. She had been taking pramipexole dihydrochloride for 78 months at a maintenance dosage of 5 mg/d, along with levodopa (600 mg/d), entacapone (1200 mg/d), and mirtazapine (30 mg/d). Her baseline UPDRS motor score (on state) was 26.

Because of disabling ICDs and punding behaviors (hypersexuality, compulsive buying, compulsive eating, and compulsive pill sorting), she was advised to gradually taper pramipexole dihydrochloride to 4 mg daily. She soon noted feeling ill, with severe anxiety and dysphoria that was initially interpreted as wearing off or undermedication. The levodopa dosing frequency was increased and selegiline hydrochloride was added; she was advised to use a medication timer and was referred for cognitive behavioral therapy. None of these interventions mitigated her symptoms.

As the taper continued, she developed new-onset panic attacks (with palpitations, shortness of breath, hyperventilation, and dizziness), agoraphobia, and generalized pain despite well-controlled motor symptoms. She was referred to a psychopharmacologist; escitalopram oxalate and alprazolam were added, with no apparent benefit. She experienced panic attacks at her office on a daily basis, during which she would call her husband and ask him to take her home from work in the middle of the day. This caused marital conflict and forced her to retire early from her position as a receptionist.

The patient repeatedly requested increases in her DRT and also self-medicated with supratherapeutic levodopa in an unsuccessful attempt to alleviate her symptoms. She reported that her medications were “not working” and that she was “stiff” and “unable to move,” but on concurrent examination she was found to be markedly overmedicated and to have severe choreiform and dystonic dyskinesias and new-onset visual hallucinations.

The treating physician (M.J.N.) suspected the possibility of DAWS and advised the patient to increase the pramipexole dosage as a temporizing measure. This produced a rapid and dramatic improvement in her symptoms. An even slower pramipexole taper was subsequently initiated, and the DAWS symptoms rapidly recurred.

Sixteen months later, she continues to take 0.5 mg/d of pramipexole dihydrochloride, with levodopa (950 mg/d) and selegiline hydrochloride (10 mg/d). Her UPDRS motor score (on state) is 28. Repeated attempts to taper pramipexole further have failed because of severe withdrawal symptoms (“I’m just so miserable. . . . I feel like a zombie. . . . I don’t feel like I can function anymore”). Her agoraphobia and panic have remitted, but she continues to experience chronic, disabling ICDs.

PATIENT 2

A 61-year-old, right-handed female artist/art teacher with a 6-year history of PD presented with left upper extremity rest tremor, rigidity, bradykinesia, shoulder pain, and hand dystonia. She had been taking pramipexole dihydrochloride for 61 months (4.5 mg/d), to which levodopa had more recently been added (300 mg/d). Her baseline UPDRS motor score (on state) was 15, her Beck Anxiety Inventory score was 8, and her Beck Depression Inventory II score was 5. For the prior 29 months, she had experienced compulsive eating, painting, cleaning, organizing, and buying (with $25 000 in credit card debt). She was advised to taper pramipexole dihydrochloride from 4.5 to 3.0 mg/d over 7 weeks and to increase levodopa to 600 mg/d. She had great difficulty tapering the pramipexole, however, because this precipitated severe anxiety, depression, agitation, fatigue, and insomnia. On several occasions, she increased the DA level back to the prior dosage and experienced concomitant improvement of these nonmotor symptoms.

Over the next year, she succeeded in lowering the dosage of pramipexole dihydrochloride to 3 mg/d. Unfortunately, she continued to experience severe ICDs and was therefore advised to continue to taper the pramipexole. This precipitated more severe anxiety and depression, uncontrollable crying spells, restless legs syndrome, and severe fatigue that did not improve with adjustment of her other PD medications. On examination, she had new-onset, severe, symptomatic orthostatic hypotension (155/96 mm Hg supine; 105/83 mm Hg seated; 88/51 mm Hg standing). By the time she had reached a dosage of 0.25 mg/d of pramipexole dihydrochloride (with 1100 mg/d of levodopa), she was unable to continue working and went on disability.

Once her pramipexole dosage was stabilized, her orthostatic hypotension remitted and her psychiatric symptoms gradually improved, although her Beck Anxiety Inventory score (13) and Beck Depression Inventory II score (4) remained higher than they were prior to the DA taper. Three years later, she continues to experience disabling ICDs with 0.25 mg/d of pramipexole dihydrochloride. Repeated attempts to discontinue pramipexole have failed because of recurrent withdrawal symptoms. She recently returned to work but has required disability accommodations despite relatively mild motor deficits (UPDRS motor score of 15).

A common feature of drugs that stimulate mesocortico-limbic dopaminergic pathways is the potential to produce addiction and withdrawal after prolonged exposure. Based on our observations, DAs are no exception.
In this article, we identify and characterize a DA withdrawal syndrome in PD. Dopamine agonist withdrawal syndrome was usually misinterpreted as undermedication or end-of-dose wearing off but in all cases proved to be refractory to levodopa, persisting even when patients were in the on state and/or markedly overmedicated. Less commonly, the symptoms were interpreted as a primary psychiatric disorder. In all cases, the symptoms temporally correlated with DA withdrawal and rapidly and selectively remitted with DA replacement, consistent with a drug-specific withdrawal syndrome.

The clinical manifestations of DAWS were highly stereotyped and closely resembled other psychostimulant withdrawal syndromes, with prominent psychiatric (anxiety, panic attacks, dysphoria, depression, agitation, irritability, fatigue) and autonomic (orthostatic hypotension, diaphoresis) manifestations. New-onset dopamine dysregulation syndrome was a common consequence of DAWS and often clouded the clinical picture. Levodopa, other PD medications, antidepressants, anxiolytics, and psychotherapy were of no benefit in mitigating DAWS symptoms.

Dopamine agonist withdrawal syndrome exclusively occurred in subjects with ICDs and thus selectively affected those with evidence of addiction. It occurred relatively frequently in our cohort, affecting 19% of subjects who tapered a DA and one-third of those who did so because of ICDs. Like other drug withdrawal syndromes, DAWS was associated with higher peak DA doses and greater cumulative DA exposure. The severity of DAWS and long-term prognosis also correlated with cumulative DA exposure; in the most severe cases, the DA could never be discontinued, leading to chronic ICDs.

One of the major barriers to the recognition and diagnosis of DAWS was that the symptoms closely resembled those of typical end-of-dose wearing off, leading to the false expectation that they would be alleviated by compensatory levodopa. This misinterpretation was compounded by the fact that some subjects used motor terminology (eg, “stiff,” “unable to move”) when referring to these nonmotor symptoms. The similarity between DAWS, dopamine dysregulation syndrome, and end-of-dose wearing off of levodopa is not surprising given that all three can be regarded as DRT withdrawal syndromes.

Impulse control disorders and other addiction disorders have previously been associated with a reward deficiency state due to dysfunction of mesocorticolimbic dopaminergic pathways. When DAs are often rapidly tapered, DAWS may underlie the psychiatric disturbances and suicide that occur after deep brain stimulation, a time between comparable doses of different DAs. Further investigation is also warranted to determine whether DAWS may underlie the psychiatric disturbances and suicidality that occur after deep brain stimulation, a time when DAs are often rapidly tapered.

Study strengths include the detailed, prospectively obtained clinical and psychiatric data and the comparison group of subjects without DAWS, which were available because the subjects were part of a prospective cohort study. Limitations include the observational nature of the study, relatively small sample size, and limited statistical power. The study was also confined to a single academic practice and thus may not be generalizable to other populations. The high prevalence of ICDs observed in DA-treated subjects in our cohort likely reflects the fact that we diagnosed all ICDs clinically, whereas prior studies have used rigorous diagnostic criteria and included only the most common types.

Our findings show that DAs have a stereotyped, substance-specific withdrawal syndrome that can cause severe, long-term psychosocial consequences. Based on these findings, we recommend close monitoring of patients—particularly those with ICDs—whenever DAs are withdrawn. In addition, physicians should strongly consider tapering DAs as soon as ICDs develop, because high cumulative DA exposure appears to increase the risk and severity of DAWS and decrease the chance of successful discontinuation of DA and resolution of ICDs.

Additional study is needed to identify other risk factors and potential treatments for DAWS and to determine whether DAWS can be provoked by switching between comparable doses of different DAs. Further investigation is also warranted to determine whether DAWS may underlie the psychiatric disturbances and suicidality that occur after deep brain stimulation, a time when DAs are often rapidly tapered.

Accepted for Publication: August 6, 2009.

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Financial Disclosure: None reported.

Funding/Support: This study was supported by the Parkinson’s Disease Foundation.

Additional Contributions: Mark Groves, MD, provided helpful critical commentary, and Jeffrey T. Thorne, MA, Michael A. Klulas, BS, Malinka Velcheva, RN, and Bill Nikolov, MD, provided technical assistance.

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(Reprinted) Arch Neurol/Vol. 67 (No. 1). Jan 2010 www.archneurol.com

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