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Should Impulse Control Disorders and Dopamine Dysregulation Syndrome be Indications for Deep Brain Stimulation and Intestinal Levodopa?

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Introduction

Among the most difficult Parkinson's disease (PD) patients to treat are those with impulse control disorder(s) (ICD's; compulsive gambling as well as compulsive sexual, buying and eating behaviors) or dopamine dysregulation syndrome (DDS; compulsive PD medication use, particularly short-acting agents)[1, 2]. Patients are often unaware of the severity and impact of their symptoms, and can be reluctant or unable to make changes in their dopaminergic replacement therapy (DRT), particularly dopamine agonists (DA's) which are most closely associated with ICD's. Evidence in support of standard pharmacological treatments and behavioral therapy for management of these symptoms is accruing, including recent preliminary studies testing amantadine[3] and cognitive behavioral therapy[4]. Despite these recent studies, the evidence in support of non-PD pharmacologic or psychosocial treatments is very limited[2].

There has been hope that newer non-pharmacologic therapies (e.g., deep brain stimulation (DBS)) or therapies with a smoother or more constant delivery of dopaminergic therapy (e.g., intestinal levodopa and long-acting DA's) would offer a definitive treatment for this complex subpopulation of PD patients. However, after initial reports of improvement in ICD symptoms in most patients undergoing DBS[5, 6], recent publications have suggested a more complex association between ICD behaviors and DBS in PD. This viewpoint will review the potential basal ganglia neural mechanisms underlying these behavioral disturbances, the experience with DBS and levodopa infusions in this patient population, and the critical need for methodological rigor in future studies of this topic.

Mechanisms Underpinning ICD's and DDS and Their Relationship to Effects of DBS Therapy

The regions of the basal ganglia most commonly implicated in the development of ICD's in general is the ventral striatum (particularly the nucleus accumbens [NAc]), which is crucial for reward system processing. Alterations in cortico-striato-thalamo-cortical circuitry also contribute to the development of ICDs, with projections involving the more ventral components of the striatum (including the NAc) more implicated in urges and impulsivity, and those engaging the dorsal striatum more implicated in motor habits and compulsivity[7–9]. The subthalamic nucleus (STN) and globus pallidus interna (GPi) have critical connectivity within the basal ganglia circuitry, inclusive of connections to both the dorsal and ventral striatum.

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It has been hypothesized that spread of electrical current into limbic STN and GPi may result in modulation of non-motor striatal circuitry, and that stimulation there may impact a neural network inclusive of non-motor cortical regions, such as the anterior cingulate cortex and the orbitofrontal cortex[10]. It is also possible that direct stimulation of the dorsal STN may impair inhibitory responses and thus contribute to development of ICD or related behaviors[11, 12].

Regarding the neural substrate of ICDs in PD specifically, a series of PET studies have found decreased D2 and D3 receptor binding potential in the ventral striatum in patients with ICDs or DDS compared with unaffected patients[8, 13, 14], and the existence of an underlying genetic susceptibility in dopamine receptors is also possible[15, 16]. Regarding networks, a SPECT study found that PD patients with compulsive gambling had a disconnection between the anterior cingulate cortex and the striatum, with gambling severity associated with perfusion deficits in a network involving multiple prefrontal cortex and striatal regions[17].

fMRI studies have confirmed disturbances in ventral striatal activity in PD ICD patients, including increased striatal reward prediction error (RPE) activity[18], diminished resting cerebral blood flow and blood oxygen level dependent (BOLD) activity during risk taking in the ventral striatum[19, 20], and in another study increased activation on exposure to ICD-related visual cues in several brain regions, including the cingulate cortex and the ventral striatum[21].

Of most relevance to this viewpoint, in a study of PD patients who underwent subthalamic nucleus (STN) deep brain stimulation (DBS) surgery, oscillatory activity in the theta-alpha band (4–10 Hz) in the ventral-intermediate portion of the STN with cortico-thalamic coherence in the prefrontal cortex was observed in patients with an ICD, but not in unaffected patients[22], leading the authors to hypothesize that excessive DRT may lead to psychiatric complications through its effects on the ventral portion of the STN and motor complications (e.g., dyskinesias) through its effects on the dorsal portion of the STN.

Addressing Impulse Control and Dopamine Dysregulation Syndrome with DBS

The management of ICD's and DDS in PD patients is complex. On the one hand, decreasing, or even eliminating specific DRT (particularly DA's for ICD's and levodopa for DDS) often leads to improvement in or resolution of ICD and DDS symptoms[16, 23]. However, many patients are unable or reluctant to make these medication changes, and a DA withdrawal syndrome (DAWS) that often necessitates reintroduction of the DA has been described[24]. At times, psychiatric medications are used, including antidepressants, antipsychotics, and anticonvulsants, but there is little current evidence to support their use in PD for this indication. Non-pharmacologic approaches may have a place, but there are challenges in using them in PD patients, especially those with behavioral disturbances or cognitive impairment.

Given these limitations in management options, it is not surprising that there has been an interest in DBS as a treatment option for ICD's in PD. This interest has been buoyed by the use of DBS as a potential treatment for addiction disorders in non-PD patients[25–32], and the link between these two sets of disorders is captured by the use of the term "behavioral addictions", which has been used to describe ICD's in the general population. Further support for this connection is the inclusion of pathological gambling with substance use disorder in DSM-5 under the category "Substance-Related and Addictive Disorders".

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In recent years there have been multiple publications detailing the use and outcomes of DBS in patients with ICD's and DDS[1, 16, 22, 33–41]. The rationale favoring this approach, particularly when applying bilateral subthalamic (STN) DBS, has been simple. Apply DBS, reduce DRT post-operatively with as good or even better control of motor symptoms, and the ICD and DDS symptoms will diminish or even resolve. However, this optimal scenario doesn't always play out in practice. Several expert groups have reported cases with a suboptimal response to both STN (unilateral and bilateral) and GPi DBS[1, 16, 36, 42, 43]. Though there is no research comparing the relative impact of STN versus GPi DBS on impulsivity and ICD behaviors, there has been speculation that there could be an advantage to the GPi target for neuropsychiatric symptoms in general[44]. Additional controlled research is needed to clarify this issue.

Additionally, and perhaps more worrisome, have been the recent reports of new-onset ICD's and DDS following DBS surgery[1, 39]. Lhommée and colleagues recently published a prospective study of 63 PD patients undergoing DBS, many of whom reported ICD or DDS behaviors prior to surgery. In this investigation, all DA's were discontinued the day prior to DBS surgery. Additionally, levodopa was significantly reduced (mean reduction in daily dose =73%) in all patients during the initial two week post-operative period[38]. With the exception of binge eating, no ICD's were encountered in the post-operative period (i.e., pre-existing cases resolved and there were no new-onset cases). The reduction in DRT, which was likely far too aggressive for routine clinical practice, likely contributed to the development of apathy in 13 participants and even attempted suicide in two patients, and rescue DRT was required for many participants. This experience highlights the critical importance that DAs and overall DRT load may play in the presence of post-operative ICD's[37], and the difficulty in stopping DA therapy. It is important to keep in mind that the Lhommée study was designed as an experiment to study apathy and medication withdrawal following DBS, and not as a method to address ICD's specifically.

Two other recent studies examined large, well-characterized DBS cohorts. In the first study of 159 patients, the authors reported two new cases of DDS post-DBS. Additionally, though ICD's resolved in two patients, there was an unexpected development of 17 new ICD cases, although the levodopa equivalent dosages (LEDD's) remained high post-operatively, probably as a result of the majority of cases being unilateral implantations. Target (STN vs. GPi) and laterality (unilateral vs. bilateral) did not affect outcome[1]. A limitation of this study was the retrospective collection of data regarding ICD's and related behaviors.

In the second study, Kim and colleagues reported similar findings in a cohort of 89 patients. Approximately 25% of their cohort manifested what they termed "impulse control and related behaviors (ICRB)" in the post-operative period. Examining the results in detail, there was a positive outcome in 13 subjects (or 65% of patients with pre-operative ICRB behaviors), with resolution of pre-DBS ICD symptoms in 6 subjects and improvement in 7 others. However, 12 patients had a negative outcome, with worsening of pre-operative ICD symptoms in 3 patients and development of new-onset ICD behaviors in 9 patients[39], despite subjects in this study experiencing a significant reduction in LEDD on average. Interestingly, in both of these studies, and consistent with others, compulsive eating either did not improve or worsened following DBS[38] [1, 39, 45]. Once again, a limitation of this study was that ICRB data was collected retrospectively and with an unvalidated instrument.

After a promising start, the cumulative experience of DBS therapy in patients with pre-existing ICD's and for DDS now appears mixed, though it must be noted that none of the described studies were designed to specifically examine the effects of DBS on ICD's or related behaviors. Though discontinuation of DA therapy, as well as very large decreases in levodopa therapy, appears to improve ICD behaviors[38], this approach is also likely to be

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associated with significant motor and behavioral side effects, as well as frank withdrawal symptoms.

The collective DBS experience highlights the need for pre-operative identification and management of ICD's and DDS. The reporting of post-operative new-onset ICD and DDS cases highlights the need for careful post-operative monitoring as well, and raises the question as to why de novo cases might occur. One hypothesis for de novo cases is that unintended spread of DBS current from the STN into adjacent limbic regions and fibers of passage could precipitate an ICD in a previously unaffected patient. In support of this hypothesis, DBS lead locations ventral or dorsal to the optimal target have been described to be associated with limbic and behavioral changes[46]. Another possibility is that new-onset cases may only occur in those DBS patients who undergo electrical stimulation, but also remain on relatively high doses of DRT post-operatively. Finally, given the great variability in assessment methods to diagnose and to properly rate severity of ICD and related symptoms in PD, it is possible that the published literature includes inaccuracies in the diagnosis of pre- and post-operative ICD disorders.

Intestinal Levodopa and Treatment of Impulse Control and Dopamine Dysregulation Syndrome

Catalan and colleagues in this issue of *Movement Disorders* address the effects of jejunal levodopa infusion on ICD's and DDS in a small study of 8 PD subjects (6 had ICD's and 3 had DDS). Dopamine infusions were administered 15 hours a day for each patient (daily dose =1007.2 ± 302.5 mg), but were not continued during sleep. DDS and ICD improved in all subjects, and concomitant punding was also noted to improve. It was unclear in this study why ICD behaviors persisted in some patients who had pre-procedure discontinuation of DA's, though in some cases continued use of high doses of levodopa and amantadine use could have contributed. Unfortunately, standardized outcome measures for ICD's or for DBS were not used in this study[47]. Clearly, additional research examining the impact of alternate delivery systems for levodopa on ICD's and related behaviors is needed.

Conclusions

Moving forward it will be critical for all DBS and levodopa infusion studies to include accepted diagnostic criteria for ICD's and DDS, assess the full range of behaviors reported to occur (including punding and hobbyism), utilize validated rating scales for ICD's and related behaviors pre- and post-operatively, and closely track all changes in PD medications post-operatively. The latter is important, given that multiple PD medications, including DA's, levodopa and amantadine to varying degrees, have been associated with ICD's and related behaviors in PD[48, 49]. Much of the available literature on the relationship between ICD's and DBS lacks methodological rigor. By prospectively monitoring patients prior to and after invasive procedures with standardized assessments, we will be better able to understand the potential benefits and risks of DBS as it pertains to ICD's and DDS.

In addition to clear improvement in existing ICD symptoms typically seen in patients who are able to tolerate significant decreases in DRT post-operatively, it will be important to study whether there may be advantages to a GPi versus STN DBS target in the ICD population. Additionally, it is also important to better understand whether new PD treatments could potentially lead to improvements in ICDs, such as non-pulsatile delivery of levodopa. Given the possible link between dopamine receptor hypersensitivity, dyskinesias, and ICD's[2], the possibility that non-pulsatile levodopa delivery could lead to improvement in both motor and non-motor symptoms warrants further study.

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The treatment of ICD's and DDS in PD patients is clinically challenging, since a delicate balance must be struck between medication adjustments, surgical intervention, and behavioral symptoms. Collectively, the existing literature does not support using existing ICD's or DDS as a primary treatment indication for DBS surgery or intestinal levodopa, but in individual patients it may be used to support the decision to pursue a surgical approach after careful evaluation of the patient and consideration of multiple factors.

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