Compulsive use of dopamine replacement therapy: a model for stimulant drug addiction?

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ABSTRACT

The compulsive use of dopamine replacement therapy (DRT) or dopamine dysregulation syndrome (DDS) is one of the behavioural disturbances reported in some patients with Parkinson’s disease (PD) and other disorders who are receiving DRT. We draw this phenomenon to the attention of the addiction field as a topic deserving of more systematic study. We outline: the clinical features, epidemiology and clinical correlates of the disorder; the unresolved issues in its definition and diagnosis; and its potential relevance to neurobiological models of psychostimulant addiction. We argue that compulsive DRT use may provide a useful model for drug addiction, while advancing our understanding of the neurobiology of addiction and improving the management of PD patients with the disorder.

Keywords Addiction, dopamine dysregulation syndrome, dopamine replacement therapy, impulse control disorders, Parkinson’s disease, psychostimulants.

INTRODUCTION

Dopamine replacement therapy (DRT) is the standard treatment for the motor symptoms of Parkinson’s disease (PD), such as tremor, rigidity and bradykinesia [1]. DRT involves administering the dopamine precursor, levodopa, or dopamine agonists (DA agonists) (e.g. pramipexole, ropinirole) to compensate for the progressive loss of dopaminergic neurones in the substantia nigra and ventral tegmental area (VTA) of the brain [2].

DRT reduces the motor impairments in PD but can also contribute to complications of advancing disease, including involuntary movements (dyskinesias), autonomic dysfunction, sleep disturbance and neuropsychiatric disturbances. Neuropsychiatric changes include adverse ‘off’ medication effects caused by drug withdrawal or the worsening of disease symptoms (e.g. dysphoria, anhedonia, fatigue, irritability, lassitude, sadness, anxiety and panic) and undesirable acute ‘on’ medication effects (e.g. hypomania, aggression and hyperactivity) [3,4].

A more rare and less well-known side effect is a pattern of compulsive and excessive use of DRT that resembles stimulant addiction [2,5]. Some patients increase their DRT medication doses well above therapeutic levels, despite experiencing increasing symptoms of drug toxicity (e.g. dyskinesias, mania and psychosis) [6,7]. They may hoard the drug, ‘doctor-shop’, resist dose reductions and exaggerate their motor symptoms to obtain increased doses of DRT [6,8]. These patients also experience withdrawal symptoms following abrupt cessation of DRT, such as anxiety, panic attacks, depression, dysphoria, agitation, insomnia, dizziness, nausea, irritability, fatigue and drug cravings [9,10]. These affective, motor and motivational disturbances are believed to be strong drivers in the progression to compulsive DRT use [10]. This withdrawal syndrome appears to be relatively specific to the type of DRT medication, and not due simply to the failure to alleviate the symptoms of the medical condition.

There is disagreement about how to describe the phenomenon. The first case reports of DRT ‘addiction’,
‘abuse’ or ‘dependence’ appeared in the early 1980s [11,12]. In 2000, Giovannoni et al. [6] suggested that the syndrome be called ‘hedonistic homeostatic dysregulation’ (HHD) in order to avoid the stigmatizing label of ‘addiction’. In 2003, Lawrence [13] renamed it ‘dopamine dysregulation syndrome’ (DDS), arguing that ‘dependence’ and ‘addiction’ were inappropriate terms because DRT medication was used to treat a progressive neurodegenerative disorder. Bearn and colleagues [14] used ‘DRT dependence syndrome’, arguing that the disorder formed part of the addiction spectrum.

We agree with Bearn et al. [14] that the abuse of dopaminergic medications in PD and other clinical disorders is a form of dependent drug abuse as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [15]. Its origins in medical treatment rather than recreational drug use should not preclude the use of the terms ‘addiction’ or ‘dependence’. However, we will use the term ‘dopamine dysregulation syndrome’ to describe the compulsive use of DRT medication throughout the paper, given its widespread use within the field.

We argue that increased attention to compulsive DRT use by addiction researchers may improve our understanding of the neurobiology of this condition and stimulant addiction more generally, and lead to better treatment of the disorder. In this paper, we review the limited observational evidence on compulsive DRT use to characterize the extent and nature of the condition, and identify some priorities for future research.

REVIEW AND ANALYSIS OF STUDIES

We searched PubMed and Web of Knowledge using the terms (where * denotes a wild card): (levodopa, L-dopa, apomorphine, dopamine*, selegiline, Parkinson*, medication, OR agonist) AND (addiction, dopamine dysregulation syndrome, DRT dependence syndrome, hedonistic homeostatic dysregulation OR abuse). Only cohort studies, case reports and series or case–control studies published in English were included in the analysis. We identified 34 relevant studies that reported on 69 DDS patients [6–8,12,14,16–43].

Prevalence

Estimates of the prevalence of DDS are uncertain. Two cohort studies estimated the prevalence of DDS as between 3% and 4% in PD patients treated with DRT [6,29]. These may be overestimates, because both studies were conducted in specialist treatment centres where such cases are likely to be referred [2,32]. It is also possible, however, that these disorders are under-diagnosed. For example, one patient was found to be taking almost double the dose recorded in medical notes [26], while another told one neurologist he was taking 2000 mg of levodopa a day while admitting to another that he was in fact taking 7500 mg/day [44].

DDS is often diagnosed when patients have emergency hospital admissions to treat the adverse effects of high-dose dopaminergic medication, such as dystonia, hypomania and psychosis [2]. Patients may be reluctant to disclose that they have increased their medication for fear of being stigmatized as ‘addicts’ (e.g. [36]), having their doses reduced or because they enjoy the effects of their medication. Case reports highlight secretive behaviour, with drug ‘stash’ found in patients’ homes, cars and hidden within clothing [12]. Studies are needed in larger samples of PD patients using standardized diagnostic criteria to estimate the prevalence of DDS.

Patient experiences

Patient reports of their experiences reveal similarities between DDS and stimulant addiction. They report the following.

1 A lack of control: patients described an ‘overwhelming desire’ to take their dopaminergic medication [39], or report ‘being grabbed by the drug’ or ‘driven to take more of it’ [12].

2 Feelings of euphoria: one patient said that he felt ‘like [he] could beat the world’ [12], another wanted ‘to feel the hit’ [6,28] while some patients report that large doses of DRT ‘kick start’ their creativity [41].

3 Improved mood and increased vitality: patients reported ‘there’s something missing. I need more energy, more pep’ [23]; ‘it improves concentration’ [17]. Some claim that increased DRT use improves their motor symptoms, although physical assessments suggest otherwise [19,20,27,28,45].

4 Overcoming aversive symptoms: many patients state that they use DRT to avoid symptoms of the ‘off state’ [12,14,22,30]. Others reported that DRT relieves pain [8,22,32,41].

Clinical correlates

Three case–control studies have reported the following risk factors for DDS: personality traits of higher novelty seeking; a history of depression, a family history of mood, psychiatric disorders and substance-induced psychotic symptoms; a history of a high alcohol intake or illicit drug use; a younger age of PD onset, dyskinesias and longer disease duration; and higher DRT dose and higher use of rescue doses [14,29,46]. Prospective studies of larger samples are needed to characterize more clearly the phenomenology, risk factors, treatment and prognosis of these disorders.
Is compulsive DRT use a model for stimulant addiction?

Type of DRT medication

DDS is more often reported in patients receiving levodopa than the DA agonists. This may be a consequence of the more rapid onset of action of levodopa, particularly in its dispersible forms. DDS is also reported in patients who use the more rapid ‘rescue’ subcutaneously injected apomorphine [6,28]. Seventy per cent (48 of 69) of the patients described using levodopa excessively, while 31% (15 of 48) of these cases also reported compulsive use of other dopaminergic medications.

DRT dose

The average levodopa dose in 29 DDS patients with data on levodopa dose was 2600 mg/day. This is approximately five times the average daily levodopa therapeutic maintenance dose of 450 mg/day [47]. Although the therapeutic range can vary widely with the progression of the disorder and the use of additional treatments. One patient was reportedly taking 7500 mg/day [32].

Onset of DDS

Time to onset of the disorder varies considerably. Borek et al. [27] reported an onset 13 years after first DRT use. Other reports have found a more rapid onset, with self-escalation of pramipexole [36] or levodopa [24] soon after [36], up to a year after [7,29,30] or a few years after initiation of DRT [7,28]. It may be difficult to identify the onset of dose escalation because of patients’ reluctance to report it, or it may occur after changes in PD medication years after the patient was first inducted onto them.

UNRESOLVED ISSUES

Management of DDS

Current clinical management includes supervised medication intake, either as an in-patient or as an out-patient with the help of family or carers [2]. Attempts to reduce or discontinue levodopa often meet with strong resistance because patients fear that this will increase aversive ‘off’ symptoms (e.g. [7,12,27,28,41]). Out-patient reductions in levodopa dosages are often followed by an escalation of DRT use and hoarding [7,12,16,19,20,23,24,32,33,37,41]. The majority of patients report relapse after dose reduction or cessation of DRT. Some patients appear to have recovered from the compulsive use of the drug [12,17,20–22,26,38], but the follow-up in these cases may have been too short to detect relapse.

Classification

There is a lack of a standardized terminology for describing these and other addictive-type behaviours in PD patients receiving DRT. For example, the label ‘DDS’ may be used to cover not only addictive use of DRT medication but also punding (repetitive stereotyped activities) and impulse control disorders (ICDs), such as gambling, compulsive eating and hypersexuality. The Movement Disorders Society revision of the Unified Parkinson’s Disease Rating Scale (MDS–UPDRS) includes a section to ‘address features of dopamine dysregulation syndrome’ (i.e. Section 1.6, Part 1) that includes questions on ICDs and punding [48]. These disorders may be related and have overlapping aetiologies, but they may also possess important behavioural and neurobiological differences and hence vary in their relationships to the various pharmacotherapies used in PD [49]. Lumping all these conditions together precludes any empirical test of these possibilities.

Diagnosis and assessment

There are no standardized diagnostic criteria or methods for assessing compulsive DRT use. Most studies have used the provisional diagnostic criteria outlined by Giovannoni et al. [6] (see Table 1). A brief assessment tool developed by Pezella et al. [50] included both ICDs and punding. More recent assessment tools for DRT-related disorders [51,52] need further validation.

The most widely used criteria for compulsive drug use by Giovannoni et al. [6] does not specify a minimum dose of DRT. They emphasize that the dose is above that required to alleviate the motor symptoms of PD. However, it is difficult to specify a supra-therapeutic dose because of the large inter-individual dose range required to control motor symptoms. In addition, different doses of DRT can

<table>
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<th>Table 1</th>
<th>Giovannoni and colleagues [6] proposed diagnostic criteria for compulsive dopamine replacement therapy (DRT) use.</th>
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<tbody>
<tr>
<td>1. Parkinson’s disease with documented levodopa responsiveness</td>
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<tr>
<td>2. Need for increasing doses of DRT in excess of those normally required to relieve Parkinsonian symptoms and signs</td>
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<tr>
<td>3. 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 behaviour, unwillingness to reduce DRT absence of painful dystonias</td>
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<td>4. Impairment in social or occupational functioning: fights, violent behaviour, loss of friends, absence from work, loss of job, legal difficulties, arguments or difficulties with family</td>
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<td>5. Development of hypomanic, manic or cyclothymic affective syndrome in relation to DRT</td>
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<td>6. Development of a withdrawal state characterized by dysphoria, depression, irritability and anxiety on reducing the level of DRT</td>
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<td>7. Duration of disturbance of at least 6 months</td>
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induce dependence because of individual differences in brain neurochemistry. There may also be milder forms of DDS arising from lower doses that escape clinical attention [29,32].

A semi-structured screening questionnaire based on the DSM-IV criteria for substance dependence was suggested by Bearn et al. [14], but this has not been used widely. Their proposed diagnostic criteria (see Table 2) require that at least three symptoms occur within a 12-month period [14]. The authors attempt to distinguish between physiological dependence—defined as the therapeutic need to alleviate clinical symptoms of PD—and ‘maladaptive, pathological, dependent patterns of use’ in which DRT use is complicated by clinical impairment and/or social harm [14]. The advantage of this approach is that it identifies features of DRT abuse that cannot be explained by difficulties in managing PD, and that may benefit from addiction treatment.

Table 2 Semi-structured questionnaire for compulsive dopamine replacement therapy (DRT) use based on DSM-IV criteria for substance dependence [14].

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<th>Questions on DRT use</th>
<th>DSM-IV feature of dependence</th>
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<tr>
<td>1. Do you ever use more DRT than is prescribed for you? If so, why?</td>
<td>Tolerance</td>
</tr>
<tr>
<td>2. What happens when you are unmedicated?</td>
<td>Withdrawal</td>
</tr>
<tr>
<td>3. Does your mood change following DRT?</td>
<td>Tolerance and withdrawal</td>
</tr>
<tr>
<td>4. Do you think that you have taken DRT in larger amounts or over a longer period than you intended?</td>
<td>Taking larger amounts than intended</td>
</tr>
<tr>
<td>5. Have you tried to control your DRT intake?</td>
<td>Desire or unsuccessful efforts to cut down</td>
</tr>
<tr>
<td>6. Do you spend a great deal of time obtaining, using or recovering from DRT?</td>
<td>Time-consuming activities to obtain and use substance</td>
</tr>
<tr>
<td>7. Has your life been affected in a negative sense by DRT use?</td>
<td>Negative physical, psychological or social consequences</td>
</tr>
</tbody>
</table>

Recent neurocomputational research suggests another hypothesis, namely, that complex changes in dopamine signalling in the basal ganglia [58] produced by chronic DRT use lead to the learning of compulsive or addictive behaviours [59]. Medicated PD patients seem less likely to learn from negative consequences, and prefer to seek rewarding stimuli [60,61], changes that are believed to be mediated by changes in synaptic plasticity (e.g. long-term potentiation) [59].

An alternative hypothesis is that impaired decision making in PD patients may also increase the risk of addictive behaviour by impairing impulse inhibition [62–64]. These cognitive deficits may reflect disruption to the reciprocal loops between the striatum and structures in the prefrontal cortex that results in dopamine depletion. Another possibility is that reduced mesolimbic dopaminergic function results in ‘reward deficiency’ in some patients [65]. Some theories suggest that the dopamine receptors D2, D3 and D4 are involved in addictive behaviours [59]. Medicated PD patients seem less likely to learn from negative consequences, and prefer to seek rewarding stimuli [60,61], changes that are believed to be mediated by changes in synaptic plasticity (e.g. long-term potentiation) [59].

BENEFITS OF REFORMING CATEGORIZATION AND DIAGNOSIS

A high research priority is to define more clearly the characteristics of DDS and assess whether these disorders may be usefully classified as a form of addiction. Terms such as ‘dopaminergic medication addiction’ (DMA) may acknowledge that these disorders lay within the addiction spectrum, draw attention to the debilitating effects of DDS and allow these patients to be diagnosed correctly and treated more effectively. Alternatively, ‘dopaminergic medication use disorder’ (DMUS) would reflect the proposed DSM-V re-classification of substance addiction and substance dependence into a single similarly named category [67]. DMUS could then be classified alongside other maladaptive patterns of substance use and be subject to equivalent diagnostic criteria. Diagnostic criteria could be developed by adapting or amending existing ones derived from the DSM-IV [14]. This would be consistent...
with practice in other areas of medicine, such as pain management.

Compulsive DRT use as a model of addiction

Further research will also evaluate whether DDS is a useful iatrogenic model of addiction that occurs in older adults in the absence of complicating polysubstance abuse [59]. It may be of value to conduct prospective functional neuroimaging studies of PD patients before and after introduction of DRT to determine whether any neurobiological findings are a cause or consequence of DRT use. This type of imaging study would be very difficult to conduct in people who become addicted to recreational drugs.

A multi-disciplinary approach into compulsive DRT use should involve collaborations between addiction and neurology researchers. This should include clinical epidemiological research that characterizes more clearly the phenomenon of DDS, identifies risk factors for these disorders and assesses their social and psychological consequences. Addiction researchers may be able to provide insights for more effective ways of treating these DRT-induced addictive behaviours, pharmacologically and psychotherapeutically.

CONCLUSION

DDS is a pattern of addictive drug use that occurs in some patients with PD treated with DRT [10]. Research into these disorders has been limited. Prospective studies and case-control and cohort studies are needed to characterize DDS more accurately and estimate its prevalence, risk factors and prognosis more reliably. Better diagnosis and characterization of these disorders (e.g. by adapting diagnostic criteria within a DSM framework) will provide a platform to test the utility of these disorders as models of addiction and lead to more effective treatments.

Declarations of interest

Dr John O’Sullivan serves on advisory boards for Boehringer Ingelheim, Hospira, Novartis and Solvay; has consultancies with Novartis and Clinical Network Services; and honoraria with Novartis, Boehringer Ingelheim and Hospira. Dr O’Sullivan has received grants from Allergan, Hospira, Ipsen, Novartis and Solvay. None of the other co-authors have any connection with the tobacco, alcohol, pharmaceutical or gaming industries.

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