Hedonistic homeostatic dysregulation in patients with Parkinson’s disease on dopamine replacement therapies

G Giovannoni, J D O’Sullivan, K Turner, A J Manson, A J Lees

Abstract
Hedonistic homeostatic dysregulation is a neuropsychological behavioural disorder associated with substance misuse and addiction. The disorder has been recognised as a consequence of dopamine replacement therapy (DRT) in 15 patients with Parkinson’s disease. The syndrome typically develops in male patients with early onset Parkinson’s disease, and can occur with orally and subcutaneously administered DRT. These patients take increasing quantities of their DRT, despite increasingly severe drug induced dyskinesias, and may develop a cyclical mood disorder with hypomania or manic psychosis. There is impairment of social and occupational functioning. Tolerance develops to mood elevating effects of DRT and a negative affective withdrawal state occurs if the drugs are withdrawn or doses decreased. The clinical features and guidelines for managing this syndrome are discussed. A set of diagnostic criteria for further investigating this condition is proposed.

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Keywords: Parkinson’s disease; levodopa; apomorphine; addiction; drug misuse

Parkinson’s disease is defined clinically as an extrapyramidal motor disorder with signs of bradykinesia, rest tremor, rigidity, and postural instability. Pathologically, the disease is characterised by the presence of Lewy bodies and selective neuronal degeneration, particularly involving dopaminergic neurons in the substantia nigra pars compacta.1 The resulting dopamine depletion in nigrostriatal projections is thought to be responsible for the motor symptoms. Cell loss in dopaminergic neuronal populations giving rise to mesolimbic and mesocortical projections has been demonstrated in Parkinson’s disease albeit it to lesser degrees than the nigrostrial pathway.1 The deficiency of dopamine in these pathways may contribute to the bradykinesia and mood disturbances which commonly accompany the motor manifestations of Parkinson’s disease.

Correcting the dopamine deficiency state in Parkinson’s disease with levodopa or dopamine agonists attenuates the motor symptoms, and may also exert a beneficial effect on the mood disorder and bradykinesia. However, dopaminergic replacement therapy (DRT) in Parkinson’s disease may also stimulate central dopaminergic pathways, which are intricately linked to the brain’s reward system and are implicated in various states of addiction.1 The stimulation of these pathways in some patients may initiate hedonistic homeostatic dysregulation, which ultimately leads to a behavioural disorder not too dissimilar from that associated with stimulant addiction. Although uncommon, this syndrome provides many challenges for the patient, their carers, and the treating physician. In this paper we describe the clinical features, propose a working definition, formulate a set of diagnostic criteria, and discuss management guidelines for this underrecognised phenomenon.

Clinical syndrome
CASE STUDY
A 41 year old man presented with mild dystonic posturing of the left arm and hand, associated with mild rigidity and bradykinesia. His parkinsonian symptoms progressed over the next 3 years prompting a trial of bromocriptine, up to 60 mg/day, with minimal therapeutic response. His medication was changed to levodopa/benserazide (madopar, 100/25 mg) three times daily in combination with 5 mg selegline twice daily with a marked response.

Over the next 3 years he increased his levodopa dose to over 1000 mg/day despite an adequate therapeutic response at lower doses. During this period peak dose dyskinesias developed. A trial of pergolide was abandoned because of severe nausea. Over the next 3 years the dyskinesias became more marked and unpredictable motor fluctuations developed. Mood swings emerged with periods of hypomania and depression. Amitriptyline up to a dose of 100 mg/day was prescribed. He increased his daily levodopa dose to 2400 mg. He was then started on intermittent subcutaneous rescue injections of apomorphine at a dose of 6 mg but his requirements increased rapidly so that within 6 months he was using more than 10 apomorphine injections/day in addition to his high levodopa intake. After 6 months of intermittent injections, a continuous subcutaneous apomorphine infusion was started at a rate of 3.5 mg/hour administered over a 16 hour period with a concomitant decrease in his levodopa dose to 700 mg/day. Over the next 5 months he doubled the rate of apomorphine infusion to 7 mg/hour and the use of additional intermittent apomorphine booster doses increased to at least 10 injections of 7 mg/day. During this period, in which he was receiving greater than 170 mg of apomorphine/day, he developed a florid hypomanic behavioural disorder with euphoria, increased energy levels, heightened libido, decreased sleep, agitation, flight of ideas, and
<table>
<thead>
<tr>
<th>No</th>
<th>Sex</th>
<th>Age of onset</th>
<th>Preceding psychiatric history</th>
<th>Family history</th>
<th>Previous history of substance misuse</th>
<th>Motor complications</th>
<th>Mood disorder</th>
<th>Behavioural disorder</th>
<th>Interpersonal relationships</th>
<th>Employment history</th>
<th>Max daily levodopa dose</th>
<th>Max daily oral dopamine agonist dose</th>
<th>Max daily apomorphine dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>36</td>
<td>Depression</td>
<td>Depression</td>
<td>Ex-smoker, moderate alcohol consumption</td>
<td>Dyskinesias, motor blocks, on-off</td>
<td>Cyclothymic</td>
<td>Hypersexuality</td>
<td>Long history of marital difficulties</td>
<td>Early retirement due to PD</td>
<td>3200 mg</td>
<td>Trials of bromocriptine (max daily dose 15 mg)</td>
<td>170 mg</td>
<td>Admitted several times with acute psychosis related to apomorphine abuse</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>39</td>
<td>Depression, panic attacks as a teenager</td>
<td>Nil</td>
<td>Nil</td>
<td>Depresion and hypomanic episodes</td>
<td>Anxiety, panic attacks</td>
<td>Nil</td>
<td>Early retirement</td>
<td>1875 mg</td>
<td>Pergolide 1.5 mg</td>
<td>138 mg</td>
<td>Admitted with hypomania and a paranoid delusional disorder</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>40</td>
<td>Mild pre-morbid depression</td>
<td>Nil</td>
<td>Nil</td>
<td>Depression</td>
<td>Exhibitionism</td>
<td>Family difficulties</td>
<td>Early retirement</td>
<td>2125 mg</td>
<td>nil</td>
<td>110 mg</td>
<td>Tried continuous apomorphine infusion but missed the &quot;hit&quot; of the intermittent injection. Despite increasing dyskinesias felt under medicated. Preferred intermittent apomorphine injections to continuous subcutaneous infusion</td>
<td></td>
</tr>
</tbody>
</table>
| 4  | M   | 42           | Nil                           | Nil            | Motor fluctuations, dyskinesias, on-off | Nil                 | Manic psychosis  | Inhibited, hypersexuality | Divorced due to behavioural disorder | Early retirement | 5900 mg | Bromocriptine 70 mg | 75 mg | }
Hedonistic homeostatic dysregulation in PD

425

phame, it also occurs with levodopa and oral
common in patients on subcutaneous apomor-
HYPERSEXUALITY

known as punding and is recognised in
recognise as irrational. This behaviour is
even though they realise that this is a senseless
infusion pumps, or other electrical equipment,
motor acts. They ritually dismantle their
which they carry out repetitive, purposeless
several interest-
ing di

which may relate to hedonistic
homeostatic dysregulation.

PUNDING

Several patients have developed stereotypies in
which they carry out repetitive, purposeless
motor acts. They ritually dismantle their
infusion pumps, or other electrical equipment,
even though they realise that this is a senseless
and unproductive habit. Patients cannot
explain why they perform these acts which they
recognise as irrational. This behaviour is
known as punding and is recognised in
amphetamine and cocaine addiction. 11 Punding
differs from compulsions in that perform-
ance of these activities is not distressing to
patients and it is only if the act is interrupted
that any compulsive urge becomes apparent. 4

HYPERSEXUALITY

Hypersexuality is common. Although it is more
common in patients on subcutaneous apomor-
phine, it also occurs with levodopa and oral
dopamine agonists. 6-8 It usually manifests as a
simple increase in libido, but, in hedonistic
homeostatic dysregulation it may also involve
inappropriate behaviour with exhibitionism,
excessive use of sex phone in lines, prostitution
services, and sex shops. Penile erections and
increased libido are both recognised side
effects of DRT in Parkinson's disease that are
mediated, at least in part, by central dopamine
D2 receptor stimulation. 6-7 These symptoms
do not imply the development of hedonistic
homeostatic dysregulation unless the addi-
tional features are also present to support the
diagnosis.

WALKABOUT

During the on or high phase these patients
become restless and develop akathisia with an
urge to walk. They walk great distances, often
wandering far from home while on. These
walkabouts tend to be aimless, devoid of specific
purpose, and associated with abnormalities in
time perception—that is, they are often unaware
of how long they have been walking for.

PATHOLOGICAL GAMBLING AND SHOPPING

Pathological gambling and uncontrollable
shopping sprees are not uncommon and have
been noted by others. 9 Several patients have
had repeated financial crises because of this
behaviour.

ALTERATIONS IN APPETITE

Alterations in appetite and weight loss com-
monly occur in this syndrome. The weight loss
probably occurs as a result of excessive motor
activity associated with drug induced dyskine-
rias and akathisia. Eating disorders, particu-
larly in hypomanic phases, are found and some
patients have developed severe and uncontrol-
lable food cravings.

DRUG HOARDING

Patients deliberately hoard extra medication,
which they surreptitiously use to supplement
their prescribed medication. This often be-
comes problematic when their supply of medi-
cation is deliberately restricted and during hos-
pital admissions. They often request additional
doses of medication despite being dyskinetic
and may retain these for future use. If
prescribed rescue medication, on an as re-
quired basis, they use it more often than
expected. Prescriptions are often obtained
from different providers. As in other addiction
syndromes, dishonesty and secrecy surround-
ing their overmedication is a feature.

SOCIAL INDEPENDENCE OR ISOLATION

Unlike subjects misusing illicit drugs patients
with hedonistic homeostatic dysregulation due
to DRT do not develop or participate in
extended social networks related to their drug
taking. Reasons for this are speculative but
probably relate to the fact that patients with
Parkinson's disease receive their medication
legally for a well defined medical condition
which is considered socially acceptable. The
need to form extended clandestine social
networks to acquire their medication is there-
fore unnecessary. There are also no under-
ground levodopa and apomorphine drug sup-
pliers and dealers. Interestingly, these patients
do not seem to misuse other substances such as
alcohol and cocaine.

Diagnostic criteria

Standard definitions of drug dependence
require a pattern of pathological use or impair-
ment in social or occupational functioning and
the presence of either tolerance or a withdrawal
state. In hedonistic homeostatic dysregulation associated with DRT in Parkinson’s disease, such definitions require modification and clarification.

PATHOLOGICAL USE
A pattern of pathological use is difficult to define as patients with Parkinson’s disease require daily use of DRT to alleviate motor impairment and are therefore unable to stop DRT. Intoxication manifests clinically as hypomanic or manic behaviour. Intoxication is usually accompanied by severe dyskinesias, which makes it difficult to see the gross behavioural disturbances. Overdosing and bingeing, defined as dosing in excess of that required for alleviating motor impairment, is central to the definition of this disorder. Setting an arbitrary quantity or dose of DRT as the cut off above which DRT misuse occurs is not justified in view of the wide individual variations in therapeutic responses to DRT. However, anything over 2000 mg levodopa or eight injections of apomorphine/day should raise suspicion.

FUNCTIONING
The disability due to Parkinson’s disease is usually sufficient in itself to affect social and occupational functioning. However, in most patients with hedonistic homeostatic dysregulation the behavioural changes have a significant additional impact on social and occupational functioning that often brings the DRT misuse to the attention of others. For example, divorce and breakdowns in close interpersonal relationships are common, financial difficulties related to compulsive spending lead to legal difficulties and inappropriate sexual advances in public and aggressive and violent behaviour has resulted in police intervention in some cases.

TOLERANCE
A strict definition of tolerance is difficult to apply in Parkinson’s disease. Dose requirements increase over time, as symptoms become more severe with disease progression. In addition, the development of tolerance to levodopa is affected by pharmacokinetic changes related to progressive dopaminergic denervation and loss of presynaptic dopamine storage mechanisms. This reduces the predictable long duration effects of levodopa and results in the development of unpredictable short duration effects and dyskinesias. In hedonistic homeostatic dysregulation there is a perceived need to increase the dose of DRT above that which is required to simply reduce Parkinsonian symptoms, possibly to extend its “use for pleasure”. An important clue to the development of tolerance to the psychological effects of DRT, despite continued motor efficacy, is the development of severe, virtually continuous, dyskinesias. Patients with hedonistic homeostatic dysregulation often only perceive themselves as being on when they have developed wild flaying dyskinesias related to a peak dose effect, which they tolerate remarkably well. Conversely, once dyskinesias have subsided, they feel off, despite continued motor efficacy.

WITHDRAWAL
Although classic withdrawal reactions from DRT are masked by the motor impairment, partial withdrawal is usually sufficient to unmask neurobehavioural features that are consistent with a withdrawal state. This typically manifests as negative affective state with dysphoria, depression, irritability, and anxiety. They display drug seeking behaviour and drug hoarding in anticipation of DRT restriction or withdrawal.

A set of diagnostic criteria is proposed in Table 2. Rather than being definitive, these provisional criteria are included to facilitate recognition of this syndrome and to stimulate further research in this area.

Management guidelines
If a pattern of levodopa misuse is established it is best to avoid intermittent subcutaneous apomorphine, as it acts as a powerful trigger in the development of hedonistic homeostatic dysregulation. Continuous subcutaneous infusion of apomorphine, however, may be appropriate. Once patients have developed the disorder the long term management becomes very difficult. Hypomanic and psychotic episodes, which can go unrecognised for weeks, are best managed with a reduction in the concentrations of DRT performed in hospital. Low to moderate dose olanzapine (2.5–10 mg/day), an atypical antipsychotic drug, is usually effective in controlling the acute psychosis. Clozapine, which may have the least extrapyramidal side effects, but requires frequent blood monitoring and the other atypical antipsychotic drugs sulpiride, risperidone, and quetiapine are appropriate alternatives. The acute psychosis usually settles rapidly, within 48 to 72 hours, to be replaced by a negative affective state with profound depression. In some cases the depression is associated with suicidal ideation and patients are best kept under close supervision during this period. Antidepressant medication is helpful in treating the mood disorder, which can have a prolonged course.

| A | Parkinson’s disease 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 behaviour, unwillingness to reduce DRT, absence of painful dystonias |
| D | 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 |
| E | Development of hypomanic, manic, or cyclothymic affective syndrome in relation to DRT |
| F | Development of a withdrawal state characterised by dysphoria, depression, irritability, and anxiety on reducing the level of DRT |
| G | Duration of disturbance of at least 6 months |

Table 2 Diagnostic criteria of hedonistic homeostatic dysregulation syndrome due to dopamine replacement therapy misuse
The management of the Parkinson’s disease in these patients is problematic. While in hospital the DRT should be rationalised to obtain an adequate motor response. Positive reinforcement, with the use of on-off diaries, helps make patients aware of their daily DRT requirements. Booster doses of medication should be avoided and if that is not possible the number of booster doses should be rationed. Patients should be watched closely for surreptitious self-medication. They should be weaned off intermittent apomorphine and if necessary transferred to continuous infusions.

On discharge the patients should receive their medication under supervision. A useful strategy has been to ration the supply of medication each patient receives. Supplying a single day’s medication at a time has proved practical. A reasonable compromise is usually possible within the confines of a predetermined daily ration. The patient’s spouse, a family member, carer, or local pharmacist are useful surrogates to control the daily administration of the medication. However, the dynamics of the relationship between patient and the provider of the medication should be carefully assessed. Patients can resort to extreme measures, often using aggressive and violent behaviour, to obtain extra medication and in some cases it is not appropriate to place carers or family members in this position. In this situation the local pharmacist, if willing to cooperate, is a more appropriate choice. Patients should undergo a formal psychiatric assessment to treat the underlying addiction. If they insight into their problem, and agree, enrolment into a drug addiction rehabilitation programme is appropriate. The prognosis is generally poor with patients often finding other sources for their medication, with relapse being the inevitable consequence.

**Discussion**

Hedonistic homeostatic dysregulation is a term coined to describe a theory of drug addiction, which integrates basic neuroscience with social psychology, experimental psychology, and psychiatry. It describes a vicious cycle of dysregulation of the brain reward systems that progressively increases, resulting in compulsive drug use and a loss of control over drug taking. In hedonistic homeostatic dysregulation there are three major components of the addiction cycle, (1) preoccupation-anticipation, (2) binge-intoxication and (3) withdrawal-negative affect. Although the psychological and behavioural effects of levodopa and its misuse are well known, hedonistic homeostatic dysregulation differs in that it describes a pathological, compulsive, behavioural disorder designed to avoid the negative withdrawal phase of DRT. The misuse of apomorphine and other dopamine agonists is less well recognised. A report emphasising the psychosexual disturbances in four patients with Parkinson’s disease on apomorphine describes features consistent with hedonistic homeostatic dysregulation.

The long duration and short duration effects of levodopa, which are found in nigrostriatal pathway function, probably occur in the mesolimbic and mesocortical dopamine pathways resulting in the unpredictable and rapid cycling mood disorder. This cyclical mood disorder may be the psychological substrate which establishes hedonistic homeostatic dysregulation. The affective and behavioural changes noted with DRT misuse are similar to those that are found with other CNS stimulants—for example, cocaine and amphetamines. The anatomical substrate for these similar effects is likely to be the mesolimbic dopaminergic projections to the nucleus accumbens where cocaine blocks presynaptic catecholamine reuptake and amphetamines promote the release of catecholamines. There is evidence suggesting these pathways have a central role in the positive reinforcing effects of all drugs of misuse.

In addition to the neuropharmacological and behavioural similarities between DRT and stimulant misuse, there is an overlap in their motor manifestations. Cocaine, amphetamine, and crack misusers may develop choreathetosis and orobuccolingual dyskinesias referred to as “crack dancing”. Cocaine exacerbates Tourette’s syndrome, idiopathic dystonia, and essential-like tremor. Acute withdrawal in stimulant misusers can result in a transient Parkinsonian state. This probably occurs as a result of compensatory mechanisms which down regulate central dopaminergic systems as a result of their overstimulation during the period of misuse. Cocaine decreases tyrosine hydroxylase activity and the density of postsynaptic dopamine receptors. Levodopa has been used as a substitute to reduce drug craving during cocaine withdrawal. DRT should therefore be classified in the stimulant category of substances of misuse alongside cocaine and amphetamine derivatives.

Intermittent subcutaneous apomorphine seems to trigger hedonistic homeostatic dysregulation in susceptible subjects. All our subjects have a history of oral levodopa misuse. In this context we have defined levodopa misuse (or harmful use) as the requirement for excessive levodopa, over and above that needed for relieving the motor affects of Parkinson’s disease, and a pattern of levodopa use which causes damage to health, either physical or mental. Physical damage occurs in the form of worsening dyskinesias and mental damage in the form of a cyclical mood disorder with or without behavioural abnormalities. Apomorphine may aggravate hedonistic homeostatic dysregulation as it provides a more effective means of stimulating central dopaminergic systems. Its rapid onset of action and peak plasma concentrations, which occurs in minutes, provides an instant “hit”. A similar phenomenon occurs with crack, the free base of cocaine, which when smoked provides a quick or instantaneous hit compared with snorted cocaine that has a more gradual onset of action. Continuous infusions of apomorphine avoid this pulsatile stimulation of dopamine receptors and if the infusion rate can be restricted, this method can be a successful compromise in some patients. The continuous stimulation of dopamine receptors achieved.
with apomorphine infusions used as mono-
therapy in advanced Parkinson’s disease may
also confer benefits in the reduction of
dyskinesias and motor fluctuations. \(^\text{31}\) The more
rapid acting formulations of levodopa may
similarly be more prone to misuse than the
slow release preparations, although we have not
directly observed this phenomenon.

Hedonistic homeostatic dysregulation in pa-
tients with Parkinson’s disease is not common,
and it is important to be aware that milder forms
with many of the features of the dysregulation
can occur without developing the full syndrome
as outlined above. We have identified 15 cases of
hedonistic homeostatic dysregulation out of a
total of 364 (113 women and 251 men) patients
with Parkinson’s disease (4%) under active
follow up. This figure is biased as our clinic
receives mainly tertiary and quaternary referrals
of patients with difficult management problems.

The true prevalence in a community based
study would be considerably lower than this.
Why some patients develop the disorder and
others do not is unknown. Patients developing
hedonistic homeostatic dysregulation from
DRT may have a premorbid psychiatric or
personality disorder, or family history of a psychiat-
ric disease predisposing them to addiction. \(^\text{19}\)

The idea that the syndrome only occur in those
with a premorbid predisposition is supported by
the number of patients who describe a mild
euphoric effect after DRT and those who try
to bigger doses to completely alleviate Parkinson-
nian features yet do not develop hedonistic
homeostatic dysregulation. \(^\text{12}\) Similarly, patients
with Parkinson’s disease treated successfully
with electrical stimulation of the subthalamic
nucleus are often reluctant to stop their
medication completely because of the beneficial
effects of DRT on mood and motivation, which
the surgical procedure does not help. \(^\text{16}\)

It may be possible to identify “at risk” patients
by using addictive personality scales to distinguish
extravert risk takers or pleasure seekers. \(^\text{31}\) Patients
with Parkinson’s disease are by and large the
opposite—that is, introverted low novelty
seekers. \(^\text{16}\) Pathological changes to the mesolim-
ic and mesocortical systems in Parkinson’s dis-
ease may modulate the addictive potential of
DRT. Preliminary PET studies suggest that nor-
mal reward circuitry involving the limbic system is
dysfunctional in Parkinson’s disease. \(^\text{7}\) \(^\text{18}\)
Progressive dopaminergic denervation will reduce
presynaptic dopamine storage mechanisms ex-
acerbating the pulsatile effects of DRT on limbic
structures. Upregulation or changes in the
sensitivity of dopamine receptors in these
systems may also play a part in the development
of hedonistic homeostatic dysregulation.

Management of hedonistic homeostatic dys-
regulation in patients with Parkinson’s disease
is extremely difficult due to the problem of bal-
ancing the drug requirement for treating the
motor aspects of Parkinson’s disease and on the
other hand limiting the drug usage to prevent
the progressive downward spiral leading to
addiction. Ideally these patients would be best
managed by specialist teams with the infra-
structure to manage and coordinate their long
term care. Neurologists should be aware of
hedonistic homeostatic dysregulation in patients
with Parkinson’s disease so that appro-
priate steps can be taken to manage it and pos-
sibly prevent its occurrence.

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