

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

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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 Tolerance develops to mood elevating effects of DRT and a negative affective withdrawal state occurs if the drugs are withdrawn or doses decreased.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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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 nigrostriatal pathway.² The deficiency of dopamine in these pathways may contribute to the bradyphrenia 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 bradyphrenia. 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.³ 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 selegiline 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

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Table 1 Patients' description

No	Sex	Age of onset	Preceding psychiatric history	Family history	Previous history of substance misuse	Major complications	Mood disorder	Behavioural disorder	Interpersonal relationships	Employment history	Max daily levodopa dose	Max daily dopamine agonist dose	Max daily apomorphine dose	Comments
1	M	36	Depression	Depression	Ex-smoker, moderate alcohol consumption	Dyskinesias, motor blocks, on-offs unpredictable dose effect	Cyclothymic	Hypersexuality	Long history of marital difficulties	Early retirement due to PD	3200 mg	Trials of bromocriptine (max daily dose 15 mg)	170 mg	Admitted several times with acute psychosis related to apomorphine abuse
2	F	39	Depression, panic attacks as a teenager	Nil	Nil	Dyskinesias, motor blocks, on-offs	Depression and hypomanic episodes	Anxiety, panic attacks	Nil	Early retirement	1875 mg	Pergolide 1.5 mg	138 mg	Admitted with hypomania and a paranoid delusional disorder
3	M	40	Mild pre-morbid depression	Nil	Nil	Dyskinesias, rapid on-offs, unpredictable dose effect	Depression	Exhibitionism	Family difficulties	Early retirement	2125 mg	nil	110 mg	Tried continuous apomorphine infusion but missed the "hit" of the intermittent injection. Despite increasing dyskinesias felt under medicated. Preferred intermittent apomorphine injections to continuous subcutaneous infusion
4	M	42	Nil	Nil	Nil	Motor fluctuations, dyskinesias, on-offs unpredictable dose effect	Manic psychosis	Disinhibited, hypersexuality	Divorced due to behavioural disorder	Early retirement	5500 mg	Bromocriptine 70 mg	75 mg	

pressure of speech. He would take long and inappropriate walks lasting up to 8 hours in the afternoons. This progressed to a full blown psychosis with florid hallucinations prompting an emergency psychiatric admission. The apomorphine was stopped with prompt improvement of his mood disorder.

Over the next 2 years he became increasingly difficult to manage with repeated admissions for manic and antisocial behaviour. The apomorphine was withdrawn and replaced with high dose ropinirole, 20 mg/day, in four divided doses. This did not stop excessive use of levodopa, which was finally restricted to a maximum of 2400 mg/day. A local pharmacist was required to assist with the rationing of his medication, which had to be dispensed on a daily basis. All rescue medication (dispersible madopar and apomorphine) was withdrawn. After apomorphine withdrawal he developed severe depression, complicated by an unsuccessful suicide attempt. His mood responded to treatment with 20 mg/day fluoxetine and he was enrolled in a drug addiction programme, which he found helpful. To control persistent disabling dyskinesias he had a left stereotactic pallidotomy with moderate therapeutic benefit. After surgery his levodopa dose could not be reduced and has subsequently been started on entacapone. There is no patient or family history of a mood disorder. He describes himself as being rather eccentric, impulsive, and has always been a novelty seeker. He has never experimented with illicit drugs.

Table 1 summarises the essential features of this case and three others who satisfy our definition of hedonistic homeostatic dysregulation due to DRT.

CORE FEATURES

In our experience patients who develop hedonistic homeostatic dysregulation due to DRT tend to be men with relatively early onset Parkinson's disease. Of 15 cases identified with overt hedonistic homeostatic dysregulation 12 have been men (80%). The mean age of disease onset of the 15 cases was 43 (SD 7.9) years. The age of Parkinson's disease onset was younger than 40 years in six cases, between 40 and 50 years in six cases, between 50 and 60 years in two cases, and in only one case was age of disease onset greater than 60 years. Early on in their disease these patients tend to self medicate and increase their DRT, often very rapidly, in large steps, and in excess of what would normally be required to control motor symptoms. Individual doses become larger and more frequent, leading to massive total daily doses of levodopa (table 1). Attempts to reduce the dose of DRT are met with strong resistance, are short lived and usually prove unsuccessful. Many of these patients develop devious strategies to stockpile medication and resist physicians' attempts to restrict their dose. By the time DRT misuse and the behavioural disorder become clinically apparent, these patients have usually developed violent and disabling, but well tolerated, drug induced dyskinesias, which do not act as a deterrent to further increases in the level of DRT. They tend to disregard dosing

schedules and start to self medicate using somatic cues, often unrelated to Parkinsonian symptoms, to take their next dose of medication. Their perception of the on state is altered and they only feel on when markedly dyskinetic.

With a progressive increase in the level of the DRT a hypomanic behavioural disorder may develop with the potential to progress into a manic psychosis. The mania is non-specific with typical psychomotor agitation, increased excitability, and elevated mood or euphoria. Patients become very demanding, with irritability and a low frustration tolerance. Their thinking is disorganised and they display poor judgement. Paranoia is common and is often directed at hospital staff, carers, and family members making the restriction of DRT more difficult. Rapid shifts in mood are common and aggressive behaviour is found in some patients. Psychotic episodes tend to resolve promptly once the concentration of DRT is reduced but are often replaced by a severe negative affective state with various degrees of dysphoria, depression, irritability and anxiety. Hedonistic homeostatic dysregulation may occur with all forms of DRT. The addition of apomorphine, as intermittent subcutaneous rescue injections or as a continuous infusion, often acts as a catalyst for the progression of the disorder. The more rapid onset of action of apomorphine compared with oral therapy seems to give these patients a subjective “kick” or “rush”, which some patients describe as a “high”. In addition to these features, we have seen several interesting behavioural disturbances in association with DRT use, which may relate to hedonistic homeostatic dysregulation.

PUNTING

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 punting and is recognised in amphetamine and cocaine addiction.^{4,5} Punting differs from compulsions in that performance 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 apomorphine, 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.^{8,9} 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.¹⁰ Several patients have had repeated financial crises because of this behaviour.

ALTERATIONS IN APPETITE

Alterations in appetite and weight loss commonly occur in this syndrome. The weight loss probably occurs as a result of excessive motor activity associated with drug induced dyskinesias and akathisia. Eating disorders, particularly in hypomanic phases, are found and some patients have developed severe and uncontrollable food cravings.

DRUG HOARDING

Patients deliberately hoard extra medication, which they surreptitiously use to supplement their prescribed medication. This often becomes problematic when their supply of medication is deliberately restricted and during hospital 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 required basis, they use it more often than expected. Prescriptions are often obtained from different providers. As in other addiction syndromes, dishonesty and secrecy surrounding 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 therefore unnecessary. There are also no underground levodopa and apomorphine drug suppliers 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 impairment in social or occupational functioning and the presence of either tolerance or a withdrawal

state.¹¹ 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.

IMPAIRMENT IN SOCIAL OR OCCUPATIONAL 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.¹² 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.

Table 2 Diagnostic criteria of hedonistic homeostatic dysregulation syndrome due to dopamine replacement therapy misuse

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| (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, 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 |

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.¹³ In hedonistic homeostatic dysregulation there are three major components of the addiction cycle, (1) preoccupation-anticipation, (2) binge-intoxication and (3) withdrawal-negative affect which result in a dysfunctional downward spiral, leading to drug addiction. Although the psychological and behavioural effects of levodopa and its misuse are well known,¹⁴⁻¹⁹ 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.²⁰⁻²¹ A report emphasising the psychosexual disturbances in four patients with Parkinson's disease on apomorphine describes features consistent with hedonistic homeostatic dysregulation.²⁰ The long duration and short duration effects of levodopa, which are found in nigrostriatal pathway function,¹² 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 reuptake²² and amphetamines promote the release of catecholamines.²³ There is evidence suggesting these pathways have a central role in the positive reinforcing effects of all drugs of misuse.¹³

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 choreoathetosis and orobuccolingual dyskinesias referred to as "crack dancing".²⁴⁻²⁵ Cocaine exacerbates Tourette's syndrome, idiopathic dystonia, and essential-like tremor.²⁶ Acute withdrawal in stimulant misusers can result in a transient Parkinsonian state.²⁷ 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 activity²⁸ and the density of postsynaptic dopamine receptors.²⁹⁻³⁰ Levodopa has been used as a substitute to reduce drug craving during cocaine withdrawal.³¹ 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.³² 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 monotherapy in advanced Parkinson's disease may also confer benefits in the reduction of dyskinesias and motor fluctuations.³³ 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 patients 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 psychiatric disease predisposing them to addiction.^{16, 19} The idea that the syndrome only occurs 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 bigger doses to completely alleviate Parkinsonian features yet do not develop hedonistic homeostatic dysregulation.¹⁶ 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.³⁴ It may be possible to identify "at risk" patients by using addictive personality scales to distinguish extroverted risk takers or pleasure seekers.³⁵ Patients with Parkinson's disease are by and large the opposite—that is, introverted low novelty seekers.³⁶ Pathological changes to the mesolimbic and mesocortical systems in Parkinson's disease may modulate the addictive potential of DRT. Preliminary PET studies suggest that normal reward circuitry involving the limbic system is dysfunctional in Parkinson's disease.^{37, 38} Progressive dopaminergic denervation will reduce presynaptic dopamine storage mechanisms exacerbating 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 dysregulation in patients with Parkinson's disease is extremely difficult due to the problem of balancing 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 infrastructure to manage and coordinate their long term care. Neurologists should be aware of

hedonistic homeostatic dysregulation in patients with Parkinson's disease so that appropriate steps can be taken to manage it and possibly prevent its occurrence.

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