

Parkinson's disease

Evidence suggests that people with Parkinson's disease who are treated with dopamine agonist drugs may have a greater incidence of impulse control disorders including compulsive gambling, hypersexuality, and potential addiction to the medication. These manifestations will have a detrimental impact on the lives of the patients as well as their families. Mel Philips and Dr Kieran Breen discuss management.

Parkinson's disease (PD) is a progressive neurological condition caused by the degeneration of dopaminergic neurons within the substantia nigra. Dopamine is responsible for the initiation and co-ordination of fine learnt body movements. PD is defined clinically by four primary symptoms; bradykinesia (slowness of movement), muscle stiffness or rigidity, postural instability and tremor. However, not all people will exhibit the four symptoms and a clinical diagnosis is usually made following the assessment of a combination of symptoms, such as is specified in the UK PDS Brain Bank criteria¹. It is estimated that 120,000 people in the UK have PD, of whom one in 20 are diagnosed under the age of 40 years².

Current treatment strategies aim to restore the imbalance of dopamine in the brain. The primary classes of drugs used to achieve this aim are:

- > Levodopa (with carbidopa)
- > Dopamine agonists
- > Catechol-O-methyltransferase (COMT) inhibitors
- > Monoamine oxidase B (MAO B) inhibitors.

Whilst the National Collaborating Centre for Chronic Conditions for the treatment of PD, produced for the NHS by the National Institute for Health and

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Clinical Excellence (NICE), does not recommend a particular drug to use as a first line treatment in symptom management, there is a tendency towards the prescription of dopamine agonists as a first line treatment in PD, particularly for people diagnosed under the age of 65 years³.

This delays the need for levodopa therapy, which frequently induces dyskinetic movements and motor

fluctuations⁴. While the stage at which the drugs are prescribed should be discussed between doctor and patient, studies have shown that an early therapeutic intervention does not have adverse effects on the long-term rate of disease progression and may indeed improve the quality of life of people with PD⁵.

Behavioural changes associated with dopamine agonists

There is an increasing body of evidence to suggest that treatment with dopamine agonist drugs may increase a person's susceptibility to altered behaviour patterns. These changes may be manifest in a number of ways although it is not uncommon for people to display more than one manifestation and there is a considerable overlap. They can be classified into three general categories:

- > Impulse control disorders (ICD)
- > Dopamine dysregulation syndrome (DDS)⁶
- > Punding⁷.

ICD includes pathological gambling⁸, compulsive eating⁹ and hypersexuality¹⁰. Although these symptoms primarily affect people on dopamine agonist therapy, evidence suggests that treatment with other anti-PD drugs, including monoamine oxidase inhibitors, may also result in the development of ICD¹¹. Indeed, pathologic gambling has also been reported in patients with restless legs syndrome treated with low levels of dopamine agonists¹².

DDS or hedonistic homeostatic dysregulation, involves the compulsive taking of dopamine replacement therapy, and usually develops as individuals take increasing amounts of drug that exceed the prescribed dose. This is considered as a form of addictive behaviour. Some people being treated with normal levels of dopamine agonists can also exhibit ICD traits similar to those observed in people with DDS⁶.

Punding refers to the repetitive use of technical equipment or the continuous sorting of hoarding of objects or pointless activities. These tend to be associated with, but are not limited to, dyskinesic movements and although they are aware of it, people tend to find it pleasurable. Quite frequently, the format

may be associated with a person's previous profession or hobby. Again, there is an overlap between the different manifestations of dopamine agonist-associated behavioural changes as those, for whom gambling is the primary manifestation, tend to have a preference for slot machines, which have a repetitive nature and may therefore be allied to punding behaviour¹³.

While the reduction or withdrawal of dopamine agonist therapy may reduce these behavioural changes¹⁴, ICD has also been associated with levodopa therapy¹⁵. The cessation of the drug potentially responsible for the abnormal behaviour should be carried out at an early stage, thus underlining the importance of the development of a close relationship between the person with PD and their clinician or a specialist PD nurse. It must be considered that alterations in a patient's medication following prolonged periods of abnormal behaviour may lead to withdrawal symptoms that are usually associated with drugs of abuse.

While initial studies suggested that four per cent of people with PD will develop ICD during the course of their treatment, more recent studies suggest that this may be a significant underestimate⁸. This is likely to be due to a reticence on the part of people with PD to report their problems to the physician. Indeed many people may be unaware of the connection with their medication.

Dopamine in the brain's reward system

In addition to its role in the co-ordination of movement, dopamine also plays a key role in the brain's reward system within the mesolimbic system of the mid-brain. This is achieved in association with the endogenous opioid neurotransmitters. Opiates have an excitatory effect on the dopaminergic neurons leading to an increase in dopamine release within the nucleus accumbens and this serves to reinforce behaviour.

The decrease in dopamine levels associated with cell loss within the nigrostriatal pathway, which underlies the motor symptoms of PD, may also influence the functioning of other brain regions. The decrease in dopamine levels may be associated with some of the non-motor symptoms such as depression

that are often associated with PD¹⁶ and also may explain why certain medication used for the treatment of PD can predispose a person to other behavioural problems associated with an excess in dopaminergic function.

The drugs used in the treatment of PD act primarily by stimulating the D1 and D2 subclasses of dopamine receptors that are involved in the control of motor function. The D3 class of dopamine receptors, however, are linked more closely with mood and behaviour and are primarily located in the mesolimbic system. Certain dopamine agonists have a high affinity for the D3 receptor and therefore may exert a greater influence on mood and behaviour. While there is no particular association between the use of selective D3 agonists and pathological gambling, a differential expression of the D3 receptors in the limbic system may account for a differential susceptibility to the behavioural effects of the drugs¹³.

Predisposing factors

It is likely that a number of factors – biological, psychological, sociological and behavioural – need to be considered when addressing the addictive behaviour associated with DDS. Psychological factors have a particular impact, as drug abuse is often considered as a way of coping with life situations, relieving worry, shame, fear and psychological and physical pain.

While most people with PD are prescribed medication to help alleviate their symptoms, only a subsection will go on to develop DDS or ICD. This strongly supports the hypothesis that there are additional factors that may influence the predisposition to the condition. This may be defined or influenced by underlying psychological symptoms or behavioural patterns thus rendering certain people to be more susceptible.

Behavioural studies have suggested that people who develop PD tend to exhibit a lower than average sensation seeking trait with a greater proportion of non-smokers and lower consumption of caffeine and alcohol¹⁷. However, people with PD who develop behavioural problems tend to have a previous history of social problems including alcohol or drug



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dependence¹⁸. Pathological gambling has also been associated with other forms of addiction such as cocaine abuse. These underlying behavioural traits may therefore be a key factor in determining the susceptibility of a person with PD to developing medication-associated behavioural symptoms. An increase in dopamine receptor stimulation associated with anti-Parkinson's medication may, in a small number of susceptible individuals, result in an increase in novelty seeking behaviours¹⁹.

Body language and oral communication can be affected in PD and some people may exhibit a lack of expression associated with rigidity in the facial muscles. This may cause an immobile or 'blank' face and an inability to smile. There may also be a problem associated with a patient's speech, sometimes making them difficult to understand and appear incoherent. Unfortunately these symptoms can often lead to negative labelling of the individual. A study on a group of patients with PD by health professionals rated them as being unhappy, bored, hostile and less intelligent. However, prior assessment of these patients showed them to be of normal intellect and without a diagnosis of depression or other psychiatric conditions². It is not surprising therefore that people with PD can feel isolated and this may help to explain why

someone with PD, with an underlying predisposition, may increase their drug dose in an effort to regain 'normality'.

Age as a factor of DDS

It is estimated that up to one in 20 people with PD are diagnosed before the age of 40 years² and people who are diagnosed with PD at a younger age appear to exhibit a greater susceptibility towards developing behavioural problems¹⁸. This may be due, at least in part, to the fact that younger people diagnosed with PD tend to be treated primarily with dopamine agonist drugs as a first line of treatment¹⁹.

Medication regimes for people with PD can often be very complex. While the consultant provides initial guidelines, the timing and dosage of the medication is often left to the individual, within limitations, in order to gain maximal therapeutic benefits. Consultation with a PD nurse specialist or other qualified professional plays a key role in this process. PD medication does not cure the condition but helps mask the symptoms. Initially, medication is likely to be prescribed at the lowest appropriate dose. However some people may perceive that, as the medication has a positive effect on their symptoms, increasing the dose of medication will further overcome the muscle rigidity, stiffness and tremor associated with PD, ultimately resulting in the development of DDS.

This may explain why factors such as age, combined with the desire to remain in employment and maintain normal relationships may also predispose an individual to increase the level of medication above that which is prescribed. However, people with DDS also tend to develop greater levels of inter-dose dyskinesias that may negate the perceived benefits of increased levels of medication. It is recommended that an evaluation for abnormal behavioural traits should be considered for younger people with PD who exhibit severe disabling dyskinesias associated with drug treatment²⁰.

Consequences of altered behavioural patterns

There is a significant overlap between behavioural disorders associated with PD medication. For example, people with DDS usually exhibit ICD or punding,

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although these can also be observed in people without the addictive DDS. Such behavioural changes will have a significant impact on the lifestyle and quality of life of not only the person with PD but also their carers and families. Pathological gambling, which is a key manifestation of ICD, has particular consequences. Therefore, further studies are required in order to further understand this condition, identify the people who may be at risk and to develop strategies to overcome the problems.

Conclusion

The majority of evidence suggests that an increased level of pathological gambling is associated with the treatment of PD by dopamine agonists. While initial estimates suggest that the prevalence of pathological gambling in people treated with dopamine agonists is 7.3 per cent (compared with a normal lifetime prevalence of 3.4 per cent¹³) this may be an underestimation due to a low level of reporting among people who have been prescribed these drugs⁸.

While the majority of cases reported to date have been associated with treatment with dopamine agonists, there have also been reports of cases associated with treatment with levodopa¹⁵ and the monoamine oxidase inhibitor selegiline, which was manifest by hypersexuality¹¹. Healthcare professionals

Key points

- > Treatment of people with PD with dopamine agonists may result in the development of behavioural changes referred to as impulsive control disorders (ICD).
- > These may be manifest in a number of ways including compulsive gambling, hypersexuality, addiction to the drugs and repetitive meaningless behaviour (punding).
- > While the reason behind this is unclear, risk factors include a younger onset of PD with a personal family history of drug abuse.
- > The development of ICD in these patients may be associated with increased dyskinetic movement.
- > Physicians should establish a dialogue with people who may be at risk of developing behavioural disorders in order that the development of the condition can be identified at an early stage.

need to have a much greater awareness of this potentially serious side effect so that they can in turn inform patients. This will help the patients and their families to recognise any changes in behaviour and seek expert advice before it becomes a huge problem.


Conflict of interest: none declared.




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