BMJ Neurology Open

At the extreme limits of L-DOPA therapy: probable dopamine dysregulation and psychiatric complications in Parkinson's disease

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To cite: Oikarinen N, Ottela E, Rönkä J, *et al*. At the extreme limits of L-DOPA therapy: probable dopamine dysregulation and psychiatric complications in Parkinson's disease. *BMJ Neurology Open* 2026;**8**:e001498. doi:10.1136/bmjno-2025-001498

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjno-2025-001498).

Received 03 December 2025
Accepted 01 March 2026

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ABSTRACT

Background Dopamine dysregulation syndrome (DDS) is an uncommon but debilitating complication of Parkinson's disease (PD), characterised by a compulsive overuse of dopaminergic therapy. Most reported cases are male and involve daily oral levodopa (L-DOPA) intake between 2000 and 4000 mg.

Methods We describe a female with young-onset PD who progressively escalated oral L-DOPA intake to a peak of 10 000 mg/day prior to subthalamic nucleus deep brain stimulation (DBS). A structured psychiatric assessment was performed after DBS. Whole-exome sequencing was conducted to evaluate possible genetic susceptibility.

Results The patient developed compulsive medication use, impulse control disorders and gingival black pigmentation with near-total tooth loss. Classical hedonistic DDS features were absent. Following DBS, the L-DOPA dose stabilised at 1800 mg/day, but psychosis emerged, requiring hospitalisation. Genetic testing did not identify a pathogenic cause for early-onset PD; a rare missense variant of uncertain significance was detected without established clinical relevance.

Discussion This case represents the highest sustained oral L-DOPA dose reported in PD. Despite lacking several core DDS features, the pattern of compulsive use suggests dopaminergic dysregulation. This case highlights limitations in current DDS criteria and suggests that contextual features, such as motor disability, psychological reinforcement and individual vulnerability, should be integrated into future refinements.

INTRODUCTION

Dopamine dysregulation syndrome (DDS), originally described as 'hedonistic homeostatic dysregulation', is a recognised neuropsychiatric complication of Parkinson's disease (PD), typically characterised by compulsive overuse of dopaminergic medication, impulse control disorders (ICDs), psychiatric comorbidities and poor adherence.[1 2] The pathophysiology of DDS is thought to involve sensitisation of mesolimbic dopaminergic pathways, consistent with the incentive sensitisation model of addiction.[3] While high-dose oral levodopa (L-DOPA) therapy has been described in association with DDS, sustained doses above 4000 mg/day (in combination with a dopa decarboxylase inhibitor) are exceptional.[4] We describe a probable DDS case with extreme L-DOPA use, behavioural complications and a rare *TENM4* variant.

CASE REPORT

A woman developed right-sided parkinsonism at the age of 29. Family history was negative. Brain MRI was unremarkable, but [^{123}I] FP-CIT SPECT showed near-complete loss of dopamine transporter binding in the left putamen and reduced binding on the right. Additional studies (cervical spine MRI, electromyography, blood, cerebrospinal fluid) revealed no clinically relevant abnormalities. Based on clinical phenotype, imaging and levodopa responsiveness, PD was diagnosed at the age of 32. Written informed consent for publication, including video, was obtained.

Therapeutic course and L-DOPA escalation

Levodopa/benserazide (300 mg/day) was initiated with good effect. Dopamine agonists were poorly tolerated (pramipexole: nausea; rotigotine: skin irritation; ropinirole: pathological gambling and compulsive shopping). Selegiline was withdrawn due to behavioural side effects.

In year four of her illness, L-DOPA escalation began in response to motor fluctuations and psychological stress. Intake peaked at 10 000 mg/day (self-report and pharmacy data) (figure 1A). National registry records showed 17 420 dispensed tablets of 100 mg levodopa/benserazide in the year before deep brain stimulation (DBS) (average 4839 mg/day, assuming full consumption). Prescriptions were obtained from multiple physicians, with early refill requests citing

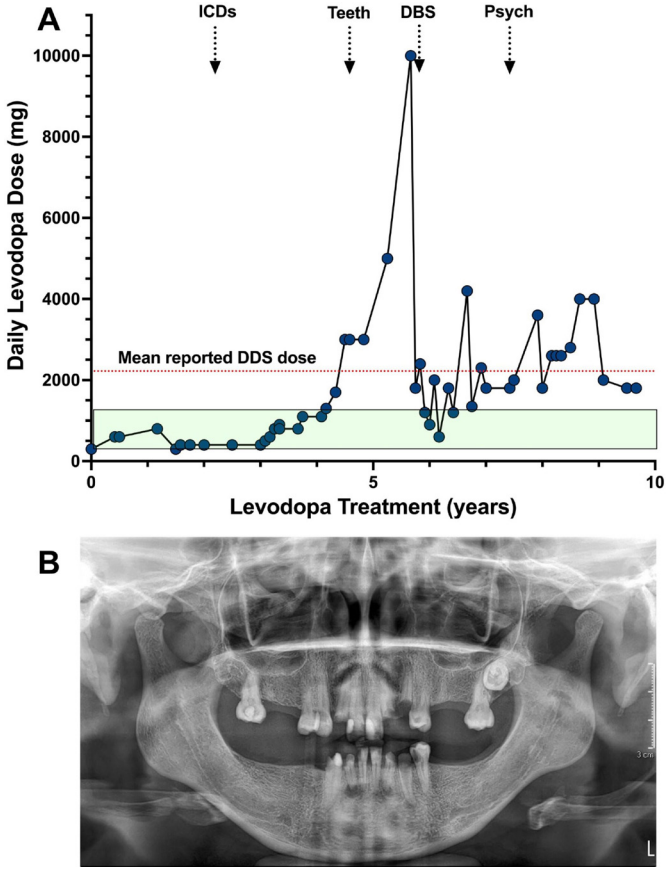

Figure 1 (A) Trajectory of daily oral L-DOPA intake (mg) over a 10-year period in a patient with young-onset Parkinson's disease. The y-axis shows daily oral levodopa (L-DOPA) dose (mg), and the x-axis represents years since treatment initiation. The dotted red line marks the mean daily L-DOPA equivalent dose (2148 mg/day) reported in a systematic review of dopamine dysregulation syndrome (DDS) cases.[4] The green shaded band indicates the typical therapeutic range of oral L-DOPA in clinical practice. Vertical arrows mark key clinical events: emergence of impulse control disorders (ICDs), onset of dental discolouration and decay (Teeth), implantation of subthalamic nucleus deep brain stimulation (DBS) and onset of psychotic symptoms requiring psychiatric admission (Psych). After DBS, L-DOPA intake decreased and stabilised at approximately 1800 mg/day. (B) Panoramic dental radiograph demonstrating severe dental decay and near-total tooth loss, reflecting the extent of dental pathology that developed during the period of extreme L-DOPA use.

shortages. She described L-DOPA as 'normalising', relieving rigidity and speech problems. There was no euphoria, but anxiety and restlessness in off-states. Dose escalation was described as necessary to avoid immobility and running out of medication.

DBS and dose stabilisation

At age 36, bilateral STN-DBS was performed for severe motor fluctuations. Postoperatively, levodopa was reduced to 600 mg/day. Later, it stabilised around 1800 mg/day, with higher doses inducing dyskinesias. Pharmacy contracts were introduced to limit dispensing. Recent video documentation shows a discrepancy in the clinical efficacy of L-DOPA and DBS: marked akinesia in medication-off/DBS-off, limited improvement with DBS-on alone, but near-normal motor function 1 hour after 300 mg soluble L-DOPA/benserazide (online supplemental video).

Psychiatric and behavioural evaluation

Post-DBS, an addiction psychiatry specialist (SN) performed a comprehensive evaluation. No substance use disorder (SUD) was found. However, the patient reported a 5-year history of problem gambling after L-DOPA initiation. There was no current or previous substance or nicotine use. She denied craving, euphoria or withdrawal.

ICD symptoms resolved after DBS, but intermittent psychosis emerged (eg, paranoid delusions, auditory hallucinations), resulting in involuntary psychiatric admissions. Psychiatric staff noted compulsive behaviours: pill hoarding, covert intake during home leaves and excessive manipulation of the DBS controller.

Dental pathology

During L-DOPA escalation, black dental discolouration along the gingival margins developed, which worsened over time. This was accompanied by extensive dental caries, eventually leading to near-complete tooth loss by the age of 39 (figure 1B). Prosthetic dental rehabilitation is planned. Although the patient reported dry mouth (xerostomia), no objective measurement of salivary quantity or buffering capacity was performed. The patient denied poor oral hygiene or major dietary changes. She reported occasional cola intake and no excessive consumption of citrus beverages, but did not specify quantities and detailed dietary records were not available. Tea consumption was not reported; she denied smoking and reported only moderate coffee use. A dental referral was made following the initial observation of tooth discolouration, but the patient did not attend until extensive dental damage had occurred.

Genetic findings

No biallelic variants in *PRKN*, *PINK1*, *DJ1* or other known early-onset PD genes were identified, and whole-exome sequencing (WES) analysis did not yield a confirmed genetic diagnosis. WES identified two rare heterozygous variants of uncertain significance (VUS). The first was a novel *TENM4* variant (c.8206G>T, p.Gly2736Cys), substituting a highly conserved glycine with cysteine. It is absent from gnomAD, with a REVEL score of 0.837, suggesting possible pathogenicity. *TENM4* has been implicated in essential tremor and certain neuropsychiatric phenotypes, with tentative links to PD,[5–7] but has not previously been linked to DDS.

The second VUS was a heterozygous *PTEN* variant (c.47A>G, p.Asp16Gly), also absent from databases. As the patient lacked phenotypic features of *PTEN* hamartoma tumour syndrome, this variant was considered unrelated to PD or DDS.

DISCUSSION

This case describes a patient with young-onset PD who developed extreme oral L-DOPA use, challenging current diagnostic frameworks for dopaminergic dysregulation. DDS has traditionally been defined as compulsive overuse of dopaminergic medication beyond motor needs, often accompanied by craving, euphoria, withdrawal-like symptoms or hypomanic states.[1] However, our patient did not present these features. A structured addiction psychiatry interview revealed no history of SUDs or hedonic reinforcement related to L-DOPA. Nevertheless, the extreme dosage, multi-provider prescription-seeking and pre-DBS ICDs indicate behavioural dysregulation.

The diagnostic challenge here illustrates a broader problem: differentiating motor-driven need for medication from behavioural dysregulation in advanced PD. The mean levodopa equivalent dose in DDS has been reported as approximately 2148 mg/day,[4] with even the highest levodopa-carbidopa intestinal gel (LCIG) or levodopa-entacapone-carbidopa intestinal gel (LECIG) infusion regimens rarely exceeding 4000 mg/day.[8] In this case, daily oral intake reached 10 000 mg, without clear evidence of malabsorption or refractory motor symptoms. This case highlights that, in some situations, extremely high LDOPA doses without an obvious medical explanation (such as malabsorption or non-responsiveness) may alone indicate dopaminergic dysregulation, even when classical DDS features are absent. Instead of hedonic reinforcement, the patient reported anxiety and helplessness during off-states and framed dose escalation as necessary to maintain motor function. This presentation aligns with the incentive salience hypothesis proposed by Berridge and Robinson, wherein compulsive drug-seeking may be driven by an amplified motivational 'wanting' response, even in the absence of hedonic 'liking'.[9] A comparable presentation has also been observed in a Swedish patient (Professor Filip Bergquist, personal communication). In that case, a patient with early-onset PD developed L-DOPA intake of up to 8000 mg/day, without overt hypomania or reward-driven behaviour. Interestingly, the compulsive levodopa use coincided temporally with periods of dysphoria and subjective motor worsening, paralleling the ICD-like compulsive drug-taking patterns observed in our case. This raises the possibility that in rare patients, excessive L-DOPA intake may overlap phenomenologically with ICDs, driven more by relief of negative affect or motor disability than by reward seeking.

Severe dental black discolouration and damage were among the most striking complications in this case, and the patient lost nearly all her teeth by age 39. The onset of visible dental damage coincided with the period of escalating L-DOPA intake; however, it is possible that carious lesions pre-existed and progressed over time, independent of medication exposure. The black discolouration may have reflected advanced caries, including root-surface involvement, rather than a direct pigmentary effect of L-DOPA. Dental caries is a multifactorial condition influenced by factors such as dietary sugar intake, acidic beverages, hyposalivation and poor oral hygiene, all of which may be exacerbated in patients with PD. As in many patients with PD, manual dexterity impairment likely reduced the effectiveness of daily oral hygiene routines. Xerostomia may be an intrinsic feature of PD and is often underreported by patients, which can complicate clinical assessment of salivary function.[10 11] While poor oral health is common in PD, due to xerostomia, manual dexterity issues and dietary changes, this degree of pigmentation and decay is unusual. L-DOPA has been associated with changes in saliva composition and pH, potentially increasing cariogenic risk.[12] Additionally, a phenomenon historically referred to as 'rusting' was reported during early L-DOPA monotherapy prior to the introduction of peripheral decarboxylase inhibitors. This involved pigmentary changes in urine, saliva, skin and hair. More recently, darkening of grey hair has been observed during L-DOPA therapy, suggesting that systemic exposure may affect peripheral pigmentation.[13] While the link between extreme oral L-DOPA intake and dental discolouration remains speculative and the finding is observational, this case highlights the need to further investigate the potential peripheral toxicities of sustained high-dose treatment.

Genetic testing revealed a previously undescribed *TENM4* missense variant, classified as a VUS. *TENM4* has been associated with essential tremor and neuropsychiatric phenotypes, with limited but emerging links to PD[5–7] and young-onset PD.[14] No known pathogenic variants were found in dopamine metabolism or receptor genes. While causal inference cannot be made, and the clinical relevance of this *TENM4* variant remains highly uncertain, it raises a speculative possibility that individual genetic architecture may contribute to rare neuropsychiatric vulnerability phenotypes in PD. We acknowledge that there is no functional evidence or previous reports supporting a link to DDS.

Taken together, this case argues for a more nuanced understanding of DDS. The patient did not meet all classical criteria, yet showed extreme medication seeking. Her presentation may represent a 'non-hedonic' or functionally driven dysregulation state, one that is underrecognised in current diagnostic models. Future revisions of DDS criteria may benefit from integrating contextual factors, such as motor disability, non-hedonic reinforcement and genetic vulnerability.

Acknowledgements We are deeply grateful to the patient for her willingness to share her case and video documentation. We also thank Dr Filip Bergquist (Sahlgrenska University Hospital, Gothenburg, Sweden) for sharing comparative clinical insights and Dr Yasser Amhdak (Turku University Hospital) for his contribution to the video recording.

Contributors VK (guarantor) collected and interpreted clinical data, prepared the video material and drafted the manuscript. NO contributed to the clinical data collection. EO and MH coordinated the acquisition and interpretation of the genetic data. JR was involved in the clinical assessment of the patient. SN performed the psychiatric evaluation. AJL provided expert guidance and critical discussion input. All authors critically revised the manuscript and approved the final version. The authors used GPT-5.1 to refine language and improve clarity. The final version was critically reviewed and edited by the authors, who take full responsibility for its content and integrity.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests The authors declare that they have no competing interests.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants. In Finland, individual case reports do not require ethical committee approval or institutional review board permission, provided that written informed consent has been obtained from the patient. This case report complies with national and institutional guidelines. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study.

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