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Dopaminergic Dysregulation as a Shared Pathway: Linking Parkinson's Disease, Substance Abuse and Behavioral Addictions

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Dopamine, a central neurotransmitter in the circuits of pleasure, movement, and motivation, represents a common node among seemingly distinct conditions: Parkinson's disease (PD), substance abuse, and behavioral addictions [1,2]. PD is a neurodegenerative disorder characterized by the loss of nigrostriatal dopaminergic neurons and the formation of Lewy bodies [3]. The introduction of levodopa in the 1970s radically changed PD management, improving motor symptoms. However, chronic exposure to exogenous dopamine also revealed significant neuropsychiatric side effects [4]. Substances such as alcohol, cocaine, amphetamines, and their derivatives act on the dopaminergic system. Abuse of these substances can cause or worsen movement disorders [1,2]. Specifically, alcohol is associated with tremors and parkinsonism.

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin, causes selective damage to dopaminergic neurons. It induces selective degeneration of dopaminergic neurons in the substantia nigra pars compacta, producing a syndrome closely resembling PD [5,6]. After crossing the blood–brain barrier, MPTP is metabolized by monoamine oxidase-B (MAO-B) in astrocytes to its toxic metabolite MPP^+. MPP^+ is selectively taken up by dopamine transporters into nigrostriatal neurons, where it inhibits mitochondrial complex I, leading to oxidative stress, energy failure, and cell death. In animal models treated with MPTP, the severity of striatal denervation correlates with the extent of dendritic spine loss, suggesting significant synaptic structural damage. This phenomenon parallels findings in patients with substance-related neurotoxicity.

The discovery of MPTP neurotoxicity revolutionized PD research, providing a robust animal model to study disease mechanisms and test potential neuroprotective therapies [7,8]. While moderate alcohol intake has been variably linked to reduced PD risk, chronic heavy use is associated with motor impairment, basal ganglia damage, and increased vulnerability to parkinsonian symptoms. Thus, alcohol's role in parkinsonism appears to be dose-dependent and multifactorial, requiring further longitudinal investigation [9,10].

Amphetamines and analogs (e.g., khat, methcathinone) can induce extrapyramidal syndromes [11]. They are potent psychostimulants that profoundly affect dopaminergic neurotransmission. Clinically, this may manifest as extrapyramidal syndromes, including parkinsonism, dystonia, and tardive-like dyskinesias. Neuroimaging studies demonstrate reduced striatal dopamine transporter binding in affected individuals, suggesting structural injury to basal ganglia pathways. Such drug-induced parkinsonism is often only partially reversible, highlighting the need for preventive strategies and early recognition in populations at risk for amphetamine or cathinone misuse [12,13].

Cocaine has been associated with tremors and signal changes in the basal ganglia [14]. It is a potent psychostimulant that blocks dopamine reuptake transporters, leading to excessive dopaminergic activity in the striatum. Acute exposure can produce tremors, choreiform movements, and dystonia, reflecting dysregulated basal ganglia circuits. Chronic use has been linked to structural and functional changes in the basal ganglia, detectable with MRI as signal abnormalities or reduced striatal integrity. These alterations likely result from dopamine-driven excitotoxicity, oxidative stress, and microvascular injury. Such findings support the hypothesis that cocaine abuse can mimic or exacerbate extrapyramidal syndromes, complicating differential diagnosis with idiopathic movement disorders such as PD [15-17].

With the introduction of dopamine agonists (bromocriptine, lisuride, pramipexole, ropinirole, rotigotine), cases of dopamine dysregulation syndrome have emerged, characterized by compulsive behaviors such as gambling, shopping, hypersexuality, binge eating, and hoarding [18,19]. These effects, although secondary to therapy, reveal a dopaminergic vulnerability shared with classic addictions. Addictive disorders are characterized by intense anticipatory responses when individuals are exposed to drug-related cues. These responses involve heightened autonomic arousal, manifested as tachycardia, sweating, agitation, and restlessness, reflecting hyperactivation of the mesolimbic dopaminergic system and its interaction with the hypothalamic–pituitary–adrenal (HPA) axis. Neuroimaging studies demonstrate cue-induced activation

in the amygdala, prefrontal cortex, and striatum, consistent with conditioned craving states [20,21]. Following this heightened arousal, many patients experience dysphoria, depression, and anxiety, likely due to rebound hypodopaminergic activity and stress pathway recruitment. Understanding these anticipatory mechanisms is critical for developing targeted interventions to reduce relapse risk. Notably, these symptoms are also observed in PD patients with impulsive behaviors [22]. The integrated analysis of PD, substance abuse, and behavioral addictions reveals a common denominator: dopaminergic dysregulation. Understanding this connection may open new shared therapeutic perspectives and targeted preventive strategies.

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