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Dopamine: "The Neurotransmitter of Desire, Movement and More"

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Abstract

Dopamine functions not only as a precursor to norepinephrine but also as a neurotransmitter closely linked to various neurological and psychiatric conditions. The dopaminergic pathways play a central role in regulating cognition and behavior in humans. Dopamine agonists (DA), which are dopaminergic drugs, are commonly used as first-line treatment for managing Restless Legs Syndrome (RLS) because they target the disrupted iron metabolism affecting dopamine neurotransmission in the brain's subcortical regions. However, patients with RLS who undergo long-term treatment with dopamine agonists often develop impulse control disorders (ICDs), a side effect of this drug class that alters neuronal signaling related to reward anticipation. The daily fluctuation of dopamine levels, combined with the use of dopamine agonists, may explain the coexistence of RLS and nighttime compulsive behaviors in patients with Parkinson's Disease (PD). In some cases, RLS and ICD-related behaviors may be two sides of the same coin: RLS requires dopamine therapy, while ICDs arise from an excess of dopamine.

Keywords: Dopamine; Neurotransmitter; Endocrine Disorders; Autoreceptor; Neuromodulators; Impulse Control disorders (ICD)

Abbreviations

DA: Dopamine; TH: Hydroxylase; VMAT2: Vesicular Monoamine Transporter 2; COMT: catechol-O-methyl transferase; MAO: Monoamine Oxidase; RLS: Restless Legs Syndrome; ICDs: Impulse Control Disorders; ADHD: Attention Deficit Hyperactivity Disorder; CSF: Cerebrospinal Fluid; DAAs: Dopamine Agonists; PD: Parkinson's Disease; DAT: Dopamine Transporter; SPECT: Single-Photon Emission Computed Tomography; ICD-RBs: Impulse Control Disorders/ Related Behaviors; PIH: Prolactin-Inhibiting Hormone.

Introduction

In 1957, Dr. Carlsson was the first to demonstrate that dopamine (DA) is a neurotransmitter in the brain, rather than just a precursor to norepinephrine. His groundbreaking work earned him the Nobel Prize in Medicine/Physiology in 2000 [1]. He also played a key role in identifying dopamine's involvement in causing extrapyramidal side effects from antipsychotic medications [2]. Since then, dopamine has been extensively researched as a critical neurotransmitter in normal brain function, with dysfunction in dopaminergic pathways now known to contribute to various conditions, including Parkinson's disease, drug addiction, and endocrine disorders.

Dopamine in the Central Nervous System

Dopamine (DA) is synthesized via the enzyme tyrosine hydroxylase (TH), which is a potential target for gene therapy and other treatments. Once synthesized, DA is packed into

synaptic vesicles by the vesicular monoamine transporter 2 (VMAT2) and stored until it is ready for release [3]. DA is then released into the synapse through exocytosis for its neurotransmitter function. Its metabolism into inactive metabolites is carried out by catechol-O-methyl transferase (COMT) in glial cells and by monoamine oxidase (MAO) [4]. The two MAO isoforms, MAO-A and MAO-B, are found in the substantia nigra and astrocytes, respectively. MAO breaks down dopamine into 3,4-dihydroxyphenylacetaldehyde, which is further degraded by aldehyde dehydrogenase into 3,4-dihydroxyphenylacetic acid. In an alternative pathway, COMT converts DA to 3-methoxytyramine, which is subsequently broken down by MAO and excreted in the urine (Figure 1).

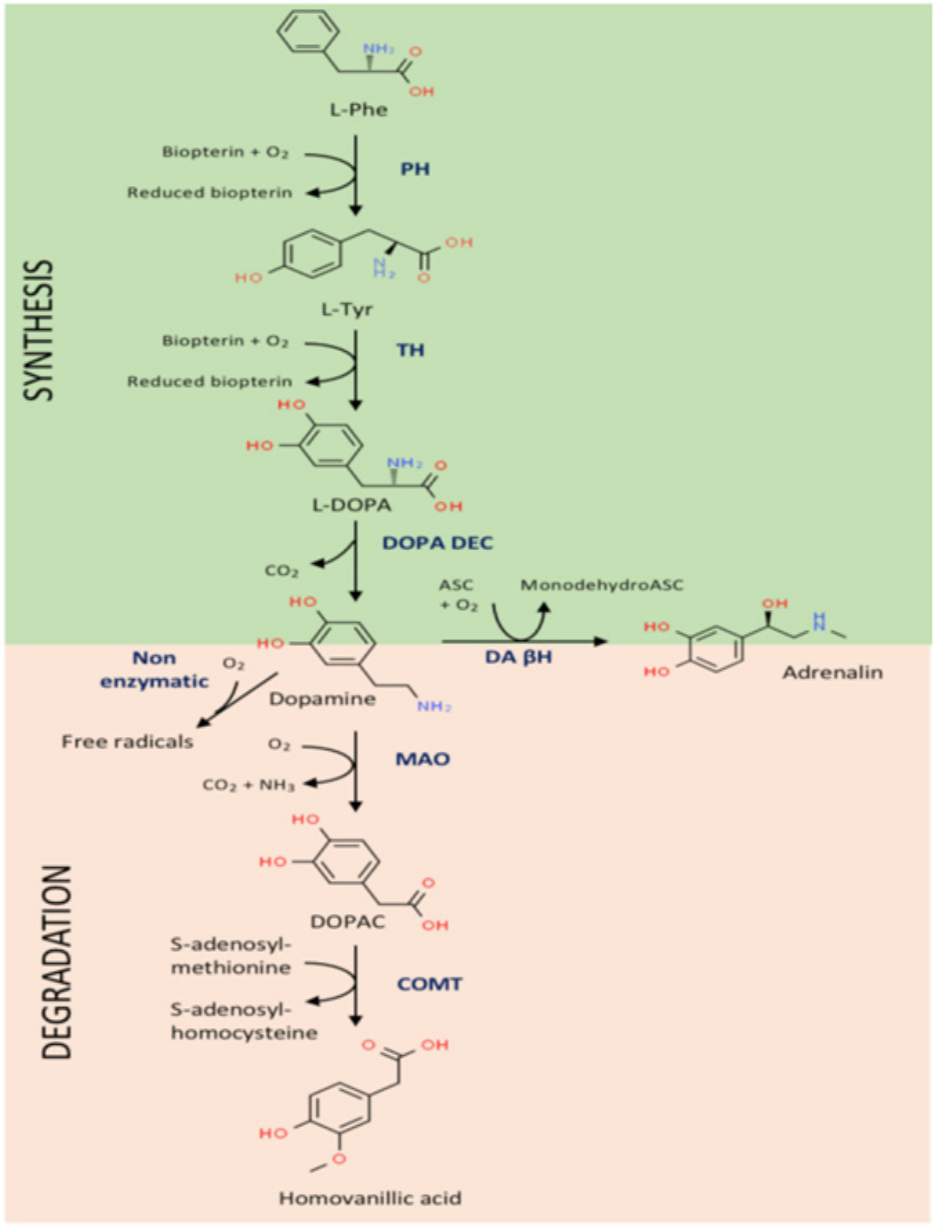

Figure 1: Biosynthesis and degradation of dopamine.

Dopamine Receptors

Dopamine receptors are a type of G protein-coupled receptor primarily found in the central nervous system. There are at least five dopamine receptor subtypes: D1, D2, D3, D4, and D5, which are categorized into two families-the D1-like family (including D1 and D5 receptors) and the D2-like family (including D2, D3, and D4 receptors) [5]. Dopamine

(DA) can bind to both postsynaptic and presynaptic receptors, creating an electrical potential. When dopamine binds to postsynaptic receptors, it transmits the signal to the postsynaptic neuron. In contrast, presynaptic dopamine receptor activity can either excite or inhibit the presynaptic cell. The inhibitory effect reduces the synthesis and release of neurotransmitters, helping to regulate normal dopamine levels [6]. This process, known as autoreceptor function, is illustrated in Figure 1.

Dopaminergic Pathways in Central Nervous System

There are three primary dopaminergic pathways in the human brain that play a crucial role in regulating cognitive and behavioral functions [7]. These pathways are integral to learning, working memory, attention, executive functions, reward, motivation, mood, and neuroendocrine regulation.

The three major dopaminergic pathways are:
i) The mesocorticolimbic pathway, also known as the reward system, transmits dopamine from the ventral tegmental area in the midbrain to the nucleus accumbens, amygdala, and frontal cortex.
ii) The nigrostriatal pathway, links dopaminergic neurons from the substantia nigra's zona compacta to the caudate nucleus and putamen.
iii) The tuberoinfundibular pathway, regulates the secretion of hormones like prolactin from the pituitary gland (Figure 2).

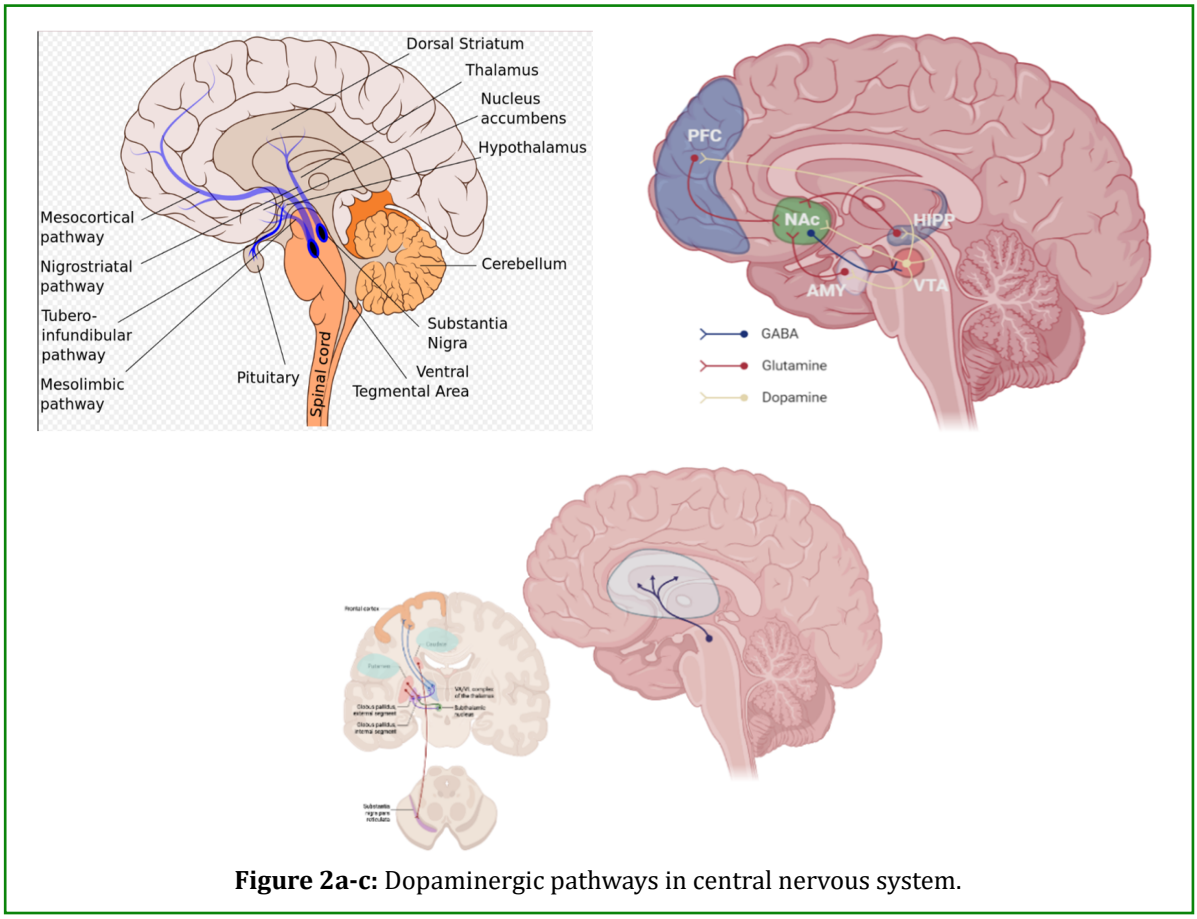

Figure 2a-c: Dopaminergic pathways in central nervous system.

Imbalances in dopaminergic signaling can lead to various disorders, some characterized by reduced dopamine levels (hypodopaminergia) and others by increased dopamine levels (hyperdopaminergia). In many cases, the pathology involves features of both extremes [8].

Hyperactivity in dopaminergic neurotransmission is linked to the development of addictive behaviors, with substances like nicotine, cocaine, and amphetamines either directly or indirectly increasing dopamine activity in the mesolimbic reward pathway [9]. This theory is supported by numerous studies showing alterations in dopamine pathways in individuals with such addictions.

Dysfunction in specific dopaminergic pathways, such as the nigrostriatal and mesocorticolimbic pathways, can result in a range of neurological disorders. These disorders span from motor impairments, such as in Parkinson's disease and

restless legs syndrome (RLS), to conditions characterized by compulsive behaviors, such as impulse control disorders (ICDs), attention deficit hyperactivity disorder (ADHD), and substance use addiction [10].

Neurobiology of Circadian Rhythm in Dopamine Release

Dopamine, a member of the catecholamine family of neuromodulators, is essential for numerous daily functions and exhibits circadian activity in the brain. Research has shown that the dopaminergic system is regulated by circadian rhythms, supported by evidence of canonical clock proteins that directly control dopamine expression and regulation within the central nervous system [11]. These circadian rhythms synchronize most biological processes through the transcription of clock genes.

Additionally, it has been observed that dopamine levels and its metabolites fluctuate with the circadian cycle, not only in humans but also in the cerebrospinal fluid (CSF) of primates and the striatum of rats. Further proof of circadian patterns in neurotransmitter release comes from the regulation of rhythms in the striatum, midbrain, and hypothalamus, which are governed by clock genes [12]. Other studies have found that dopamine receptor sensitivity increases at night within the tuberoinfundibular-dopaminergic system [13].

This diurnal variation results in greater dopamine release during the day, leading to different effects on dopamine receptors depending on the time of day. Sleep is promoted by lower dopamine levels acting on D2 receptors at night, while higher dopamine levels during the day stimulate wakefulness through D1 receptors (Figure 3).

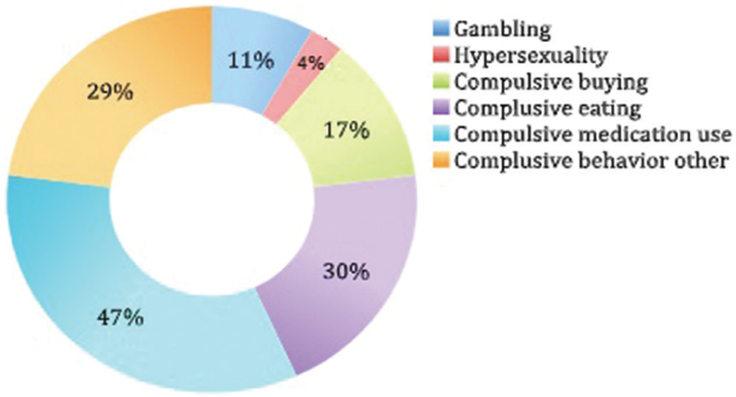

Figure 3: ICD-RBs type and frequency noted in the study cohort.

Dopamine Agonists

Dopamine agonists (DAAs) are a class of drugs that target one of two families of dopamine receptors: D1-like and D2-like. Their interaction results in increase in dopamine activity influencing various physiological and psychological processes. DAAs are typically categorized into two types: ergoline and non-ergoline derivatives that bind to dopamine receptors [14]. Ergot derivatives such as bromocriptine, pergolide, and cabergoline preferentially target dopamine D2/3 receptors over D1 receptors, but their clinical use is often limited due to side effects. Newer, non-ergoline agonists are better tolerated, selectively binding to D2 and D3 receptors with a high affinity and having minimal interaction with other receptors [15,16]. As dopamine agonists mimic the actions of dopamine action hence stimulate dopamine receptors and modulate neural pathways for reward and motor control.

The primary uses for dopamine agonists include treatment of Parkinson's disease (PD), restless legs syndrome (RLS), and hyperprolactinemia. Pramipexole and ropinirole, which have a strong affinity for D3 receptors located in the mesolimbic system, are particularly favored for managing PD and RLS [17]. Using dopamine agonists in movement disorders result in improved motor function, enhanced cognitive functions and improved quality of life. One must be careful regarding the side effects of continued use of dopamine agonists such as nausea, vomiting, dizziness, orthostatic hypotension, impulse control disorders as well as excessive day time sleep. Future holds in developing newer more selective dopamine receptor modulators, investigation their role in depression and ADHD. Dopamine agonists elucidating dopamine's role in various neurological and psychiatric disorders hence understanding their mechanisms and clinical implications can optimize treatment strategies.

Dopamine antagonists are agents that block dopamine receptors reducing dopamine activity and modulate neural pathway. Therapeutically they are useful for schizophrenia,

bipolar disorders and tics disorders. Commonly used dopamine antagonists agents are haloperidol, chlorpromazine, respidone, and olanzapine. One should be watchful regarding the side effects of dopamine antagonism such as extrapyramidal symptoms (tremor, rigidity, oral dyskinesia), sedation and hyperprolactinemia.

Restless Leg Syndrome

Restless leg syndrome (RLS), also referred to as Wills-Ekbom disease, is a prevalent neurological disorder first described by Sir Thomas Willis in 1672. He said that "there are great disturbance of the limbs affecting sleep and these are disturbances are most painful." Although the clinical understanding of RLS has evolved, the core features Willis identified remain largely unchanged [18,19]. The prevalence of RLS varies worldwide, ranging from 7–10% among Caucasians, 0.1–12% in Asian populations, 10% in the United States, 10–15% in Canada, and 5.5% across Europe [20-22].

RLS is characterized by an irresistible urge to move the legs while at rest, with symptoms often relieved through physical activity and primarily occurring at night. Though the disorder mainly affects the legs, other body parts such as the arms, shoulders, neck, face, abdomen, and genitals can also be involved [18,21].

The iron-dopamine hypothesis suggests that RLS is related to regional iron deficiency, which impairs dopamine neurotransmission in subcortical brain regions. Genetic factors influencing iron metabolism may also play a role, highlighting the importance of understanding both iron and dopamine systems in RLS treatment [23].

Dopamine and RLS

The pioneering research by Ekbom and Nordlander on RLS highlighted the involvement of iron in the disease's early stages. Later imaging studies reinforced the strong link between iron metabolism and RLS symptoms [24]. Moreover, genome association studies have identified RLS risk alleles in five genomic regions related to BTBD9, PTPRD, MAP2k/SKOR1, MEIS1, and TOX3/BC034767 [25,26].

Supporting the dopamine disturbance hypothesis are findings that dopaminergic drugs, particularly dopamine agonists, alleviate RLS symptoms, while dopamine antagonists that cross the blood-brain barrier worsen symptoms. Domperidone, which does not cross the blood-brain barrier, shows no such effect, further strengthening this hypothesis. Additionally, pharmacological studies have demonstrated elevated 3-orthomethyl dopamine levels in cerebrospinal fluid (CSF), correlating with increased levels of the dopamine metabolite homovanillic acid. This suggests heightened tyrosine hydroxylase activity leading to increased dopamine production. Dopaminergic A11 cells, located in the midbrain and projecting throughout the spinal cord, are the primary source of dopamine in the spinal cord and regulate sensory, motor, and autonomic functions. Some researchers speculate that A11 cells may also contribute to RLS pathophysiology, though more studies are needed to confirm this [27,28].

Imaging studies have also shown that reduced fluoro-l-dopa (f-DOPA) uptake indicates rapid dopamine turnover, supporting the dopaminergic hypothesis. Animal studies have found decreased dopamine transporter (DAT) levels, particularly membrane-bound DAT, and reduced D2 receptors in iron-deficient neurons, similar to those seen in RLS [29].

Circadian Rhythm of Dopamine Levels in RLS

Dopaminergic agents may alleviate RLS symptoms due to their influence on neural networks rather than by addressing a dopamine deficiency. The effectiveness of dopaminergic agonists that cross the blood-brain barrier in reducing RLS symptoms suggests that the cortico-cerebral dopaminergic system is more involved in RLS pathophysiology than the peripheral nervous system.

Pharmacological studies indicate an excess of dopamine in the brain in RLS patients, making levodopa treatment seemingly counterproductive. This paradox can be explained by the circadian rhythm observed in both dopaminergic activity and RLS symptoms. Dopamine levels naturally rise in the morning and fall in the evening and night. During the day, the post- synaptic response in RLS is adequate, but at night, despite the overall dopamine surplus, there is an apparent deficit, leading to the characteristic nighttime RLS symptoms alternating with wakefulness [30,31].

Administering low doses of dopamine at night may provide temporary relief but can lead to a worsening cycle of downregulation, ultimately exacerbating RLS symptoms. This phenomenon, known as augmentation, initially presents as tolerance, with patients requiring increasing doses for the same effect. Over time, however, the symptoms worsen, particularly during the day, causing patients to become dependent on medication to avoid withdrawal symptoms [32-34].

Augmentation is a common issue in long-term dopaminergic treatment for RLS. Patients experience more severe symptoms, such as earlier onset of symptoms during rest, spreading of symptoms to other body parts, increased intensity, and shorter medication effectiveness. Up to 60%–85% of levodopa-treated patients, and 11%–24% of those treated with dopamine agonists, experience augmentation. A recent cohort study found that 56% of RLS patients showed

signs of possible augmentation, while only 24% were unaffected [35,36].

Impulse Control Disorders

Impulse Control Disorders (ICDs) are a varied group of conditions now classified under "Disruptive, Impulse Control, and Conduct Disorders" in the DSM-5. These psychiatric disorders are marked by impulsivity and the inability to resist urges or impulses. ICDs are a significant and often devastating side effect of long-term dopaminergic therapy, particularly in genetically predisposed individuals with co-existing personality traits.

Epidemiological studies show that ICD prevalence varies based on social, economic, and environmental factors, with specific manifestations such as hypersexuality, gambling, and compulsive eating influenced by geographic and study criteria [37-39]. In Parkinson's disease (PD) patients, ICD prevalence ranges from 2.6% to 34.8%, with rates as high as 39.1% among those treated solely with dopamine agonists. A study in the Asian subcontinent on long-term dopamine agonist users found compulsive medication use (47.4%) to be the most common abnormal behavior, followed by compulsive eating (29.4%), compulsive buying (17.6%), gambling (11.7%), hypersexuality (3.9%), and other compulsive behaviors (29.8%) [39,40].

In Restless Legs Syndrome (RLS) patients, ICD prevalence is lower, ranging from 7.1% to 11.4%. Interestingly, Bayard et al. found that the prevalence was lower in patients taking dopamine agonists (2%) compared to drug-free patients (2.5%), though the dopamine agonist doses in their study were significantly lower than in other RLS studies [35,36]. In prolactinoma patients treated with dopamine agonists, two studies have reported ICDs. One study observed ICDs in two out of 20 patients, while in the other, a quarter of the sample was affected [41].

Impulse Control Disorders

Impulse Control Disorders (ICDs) are a recognized class effect of dopamine agonists, with the relative risk ranked as follows: pramipexole > ropinirole > rotigotine > apomorphine. The exact cause of this variance is unclear, but studies suggest that dopamine agonists with a higher affinity for the D3 receptor are more strongly associated with ICDs than less selective agents. In fact, the relative risk of ICDs appears to correlate with D3 receptor affinity. ICDs, such as gambling disorder, compulsive sexual behavior, compulsive shopping, binge eating, and punding, are also common in Restless Legs Syndrome (RLS) patients treated with dopamine agonists, with prevalence rates between 7% and 16% [42-44].
Moreover, individuals with Parkinson's disease (PD) who receive dopaminergic medications-particularly younger male patients with an addictive pre-morbid personality-are at a heightened risk of developing ICDs and related behaviors (ICD-RBs) [45]. Previous studies have demonstrated that dopamine agonists are associated with ICDs not only in PD but also in RLS and occasionally in hyperprolactinemia.

Pulsatile administration of dopaminergic drugs can sensitize the limbic ventral striatum and the motor dorsal striatum, potentially leading to a shift from apathy to ICDs and from bradykinesia to dyskinesia from a motor perspective [46]. On a neurobiological level, dopamine agonists alter the neuronal signaling of reward expectation (by hyperactivating the mesolimbic dopaminergic system) and reduce negative reinforcement in feedback-based learning, increasing vulnerability to ICDs. Studies have shown decreased neuronal activity and impaired response inhibition in regions such as the lateral orbitofrontal cortex, rostral cingulate zone, amygdala, and external pallidum, contributing to pathological gambling in individuals on dopamine agonist therapy [47].

Dopamine Imaging in ICD

An imaging study using single-photon emission computed tomography (SPECT) of the dopamine transporter (DAT) found reduced tracer binding in the right ventral striatum in Parkinson's disease (PD) patients with impulse control disorders (ICDs). This suggests either a reduction in mesolimbic projections or lower DAT expression on presynaptic terminals. Another SPECT study reported reduced tracer uptake in the left putamen and left inferior frontal gyrus in PD patients with ICDs, compared to those without ICDs. This "dopamine fronto-striatal disconnection syndrome" has been considered a biological explanation for ICD symptoms in PD patients [48].

Association Between ICD and RLS: Coexistence or Correlation

Restless legs syndrome (RLS) and impulse control disorders/related behaviors (ICD-RBs) may represent two sides of the same coin: RLS typically emerges as a result of dopamine treatment, while ICD-RBs stem from excessive dopamine. Studies also indicate that some untreated RLS patients may exhibit addictive behaviors, such as gambling, suggesting that these impulsive actions could be linked to the patient's predisposition rather than just dopaminergic therapy [40].

Previous research has shown a relationship between RLS and ICDs in people with Parkinson's disease (PwPD). In one observational study, it was reported that 53.6% of PwPD exhibited at least one ICD-RB, with compulsive drug use being the most common. Additionally, 18.9% of the participants had RLS, and 12.6% of PwPD had both RLS and at least one ICD-RB. The most frequently observed ICD-RBs

in patients with RLS were gambling (27.7%) and compulsive eating (44.4%), with hypersexuality being the least common, reported by only 5.5% of patients [40].

The study also found a notable association between psycho-behavioral traits, such as gambling and compulsive eating, and PD patients who had RLS, compared to those without RLS. It was suggested that the temporal pattern of these behaviors may explain the association. For instance, 80% of patients with compulsive eating reported increased nocturnal eating, while gambling behavior tended to occur in the late evening or night. This could disrupt sleep, leading to a stronger connection between these behaviors and RLS. Conversely, RLS- related sleep disturbances, including poor sleep quality and daytime drowsiness, might increase the likelihood of impulsive actions in PwPD. Previous observational studies have also reported a link between sleep disruption and impulsive behaviors in PwPD [40].

Dopamine release follows a circadian rhythm, with lower levels promoting sleep through D2 receptors at night and higher levels enhancing wakefulness via D1 receptors during the day. This fluctuation in dopamine, along with the use of dopaminergic medications, might explain the coexistence of RLS and nocturnal compulsive behaviors in PD patients. It suggests that gambling, nocturnal eating, and RLS could be related to the sleep-wake state and the circadian rhythm of dopamine pathology.

In the later stages of PD, dopamine deficiency in the nigrostriatal pathway may cause denervation hypersensitivity of D1 and D2 receptors in the dorsal striatum. Dopaminergic medications can lead to a relatively hyperdopaminergic state, causing desensitization or down-regulation of D2 receptors. Alongside circadian dopamine fluctuations, this can result in oscillations of dopamine levels, creating a pattern of ICD-RBs and RLS. The long-term use of dopaminergic treatments or the progression of the disease itself may contribute to the development of both RLS and ICD-RBs in PwPD [49-51] (Figure 4).

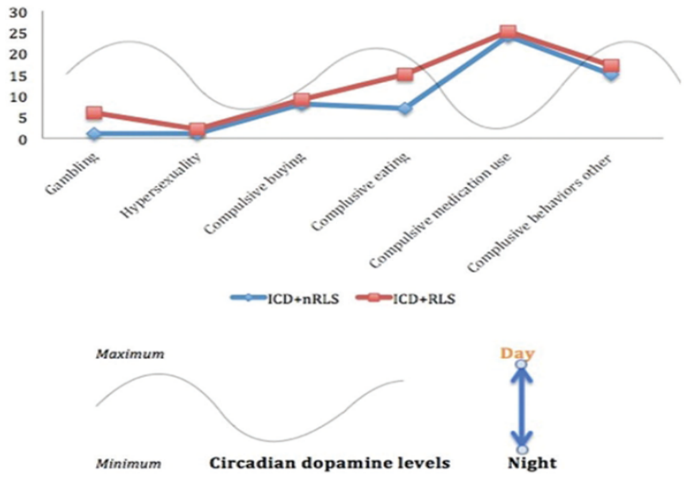

Figure 4: Depicting the co-occurrence of ICD-RBs with RLS in cohort of Parkinson disease with circadian levels of dopamine; black curved line depicting circadian levels of dopamine.

This cycle of relative dopamine deficiency amidst hyperdopaminergic states may explain the co-occurrence of RLS and ICD-RBs. Further research is needed to explore this potential circadian modulation of ICDs.

Dopamine in Neurological and Neuro psychiatric Disorders

Dopamine is a key neurotransmitter involved in regulating neurons, synaptic processes, and motor control. It plays a significant role in the development of several neurological and neuropsychiatric conditions, including Parkinson's disease, Huntington's disease, ADHD, addiction, and schizophrenia [52].

Dopamine Deficiency

A lack of dopamine in brain pathways leads to symptoms like low mood and lack of motivation, contributing to conditions such as depression, schizophrenia, and psychosis. Schizophrenia is particularly linked to dopamine dysfunction, and many antipsychotics used for treatment work by reducing dopamine activity [53,54]. Parkinson's disease (PD) is a neurodegenerative disorder caused by the loss of dopamine-

producing neurons in the substantia nigra, leading to motor issues like resting tremors and difficulty with movement. Treating motor symptoms in PD often involves dopamine replacement through L-DOPA, a precursor that crosses the blood-brain barrier and converts into dopamine in the brain.

Additionally, dopamine acts as the primary regulator of prolactin secretion from the anterior pituitary gland. The hypothalamic arcuate nucleus produces dopamine, which inhibits prolactin release through specific pathways. Without dopamine, prolactin is secreted continuously, giving dopamine the title of prolactin-inhibiting hormone (PIH) or prolactostatin.

Dopamine Excess

Excessive dopamine activity can trigger pleasurable experiences such as eating, sex, winning, or listening to music. It also responds strongly to addictive substances like opiates, alcohol, and cocaine, producing effects stronger than natural rewards and without inducing satiety. Elevated dopamine levels are associated with impulsive behaviors, such as increased competitiveness, aggression, and conditions like ADHD, binge eating, addiction, and gambling.

Dopamine in Clinical Practice

Dopamine is often used as a peripheral vasostimulant in medical emergencies, such as low heart rates and cardiac arrest, especially in neonatal intensive care through intravenous infusions. Naturally increasing dopamine levels can be achieved by consuming foods rich in L-Tyrosine, which is needed for dopamine synthesis. These foods include almonds, avocados, bananas, beef, chicken, and eggs. Supplements like turmeric, vitamin D, magnesium, and omega-3s are also linked to increased dopamine levels. In conclusion, dopamine is a crucial neurotransmitter that underpins various aspects of behavior, learning, pleasure, reward, and motivation.

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