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Table of Contents

Abstract

Parkinson's disease (PD) is commonly treated with dopaminergic therapies that effectively address motor symptoms; however, their effects on the non-motor aspects of one's life remain underexplored. By systematically synthesizing data across mood, sleep, and cognition, this study intends to evaluate how levodopa, dopamine agonists, and monoamine oxidase B (MAO-B) inhibitors influence non-motor symptoms and overall quality of life in patients with PD. Data were collected from nine studies published between 1999 and 2025, spanning longitudinal observational, cross-sectional, within-subject ON/OFF, randomized crossover, systematic review, and case series designs to ensure that both the breadth and depth of current research are considered. Dopamine agonists are associated with reduced motivational and apathy symptoms, while MAO-B inhibitors are associated with reduced depressive symptoms; anxiety scores were higher in the ON medication state. Moreover, higher dopaminergic exposure was associated with impulse control behaviors. Each type of therapy was associated with variable cognitive effects. Ultimately, Levodopa was associated with benefits in attention, processing speed, working memory, executive function, and episodic memory but with worsened cognitive inhibition. At the same time, rasagiline showed benefits in working memory and verbal fluency, and pramipexole and selegiline were linked to worse episodic memory, impulse control, global cognition, and concept formation. Treatment universally worsened sleep outcomes; total dopaminergic dose was a stronger predictor of excessive daytime sleepiness than agonists. Although these findings are substantiated, there remains a lack of comparative evidence in current PD literature, so we have a limited understanding of the long-term trade-offs between therapy type and quality of life. This study therefore calls for more patient-centered treatment strategies in the future to address both the motor and non-motor manifestations of PD.

Introduction

Parkinson's disease (PD) has traditionally been understood and treated as a motor disease. It is characterized by tremors, rigidity, and bradykinesia. As a result, most standard treatments, particularly dopaminergic therapies such as levodopa, dopamine agonists (e.g., pramipexole), and monoamine oxidase B (MAO-B) inhibitors (e.g., rasagiline, selegiline), have been developed to restore dopamine levels and improve motor function only, with no consideration of non-motor effects. While these medications are often effective in managing motor symptoms, they also influence non-motor aspects of one's life. These include mood, sleep, and cognition, each of which is affected in complex and sometimes inconsistent ways and plays a critical role in the patient's well-being (Deuel & Seeberger, 2020; Roy et al., 2018).

Recent research has increasingly emphasized that non-motor symptoms are a major contributor to the overall effects of PD as a disease and reduce quality of life in patients with PD. Symptoms such as depression, anxiety, sleep disturbances, fatigue, and cognitive impairment can persist even when motor symptoms are controlled (Dhar et al., 2025). Although some dopaminergic treatments may temporarily relieve certain non-motor symptoms by increasing dopamine signaling, they can also introduce adverse effects. Fluctuating dopamine levels produced by medications such as levodopa have been linked to complications including dyskinesia and disrupted sleep-wake cycles (Suzuki, 2021). Dopaminergic tolerability itself also differs across parkinsonian disorders (Vasta et al., 2017). Non-motor symptoms have additionally been linked to dysfunction in neurotransmitter systems other than dopamine, suggesting that treatments targeting dopamine alone may be insufficient to address PD (Deuel & Seeberger, 2020). This highlights the limitations of current treatment approaches and shows that the current approaches may only partially address the broader neuropsychiatric effects of PD.

The current literature lacks understanding of how different Parkinson's medications and treatments affect non-motor symptoms and how these effects translate to overall quality of life. Many studies focus on individual symptoms or specific drugs in isolation, but do not compare the possible therapies available. There has also been limited evidence examining the tradeoffs between therapeutic benefits and non-motor side effects for long-term patient well-being.

To address this gap, our research question asks: how do commonly used Parkinson's medications, including levodopa, dopamine agonists, and MAO-B inhibitors, impact non-motor symptoms and overall quality of life? We synthesize findings across multiple non-motor aspects of life and across the three most commonly prescribed medication classes. This study aims to provide a more comprehensive perspective on the broader impacts of PD treatment and to identify areas where more targeted and effective therapeutic strategies are needed.

Background

In recent years, Parkinson's disease research has expanded beyond its traditional focus on motor symptoms to emphasize the significant impact of non-motor symptoms such as sleep disturbances, mood disorders, and cognitive impairment. Although the use of dopaminergic medications like levodopa and dopamine agonists remains the primary treatment option, researchers are paying an increasing level of attention to the degree to which these medicines can impact non-motor areas, observing that they can reduce apathy or anxiety but also trigger side effects including daytime drowsiness or cognitive changes. Validated patient-reported instruments are commonly used in contemporary studies; most prominently, the Non-Motor Symptoms Scale and the Parkinson's Disease Questionnaire are used to measure symptom burden and quality of life. Interest in adjunctive and non-dopaminergic interventions targeting additional neurochemical pathways beyond dopamine is also growing. These research efforts

combine to reflect a broader shift toward understanding Parkinson's disease as a complex, multisystem condition that requires treatment strategies addressing both motor and non-motor experiences (Deuel & Seeberger, 2020).

Several themes also emerge across the broader literature. First, non-motor fluctuation is increasingly considered a treatment target in its own right, with add-on therapies increasingly evaluated for mood and sleep rather than only motor symptoms. Second, the evidence for sleep-wake cycles is rather thin despite sleep problems being among the most frequently reported non-motor complaints in PD. Whether and how medications worsen sleep cycles remains to be researched. Third, there is growing recognition that non-motor symptoms are not produced by dopamine loss alone, leading to increasing interest in serotonergic, noradrenergic, and cholinergic targets for PD as a whole.

The pharmacological rationale behind dopaminergic therapy also helps explain the stratified non-motor effects. PD, as it is most directly associated with the loss of dopamine in motor-related areas of the brain, is usually treated with dopaminergic medications designed to replace what has been lost. Because dopamine itself cannot cross the blood-brain barrier, levodopa is used as a precursor. Levodopa floods striatal receptors to leave them depleted between doses once the brain has largely stopped producing dopamine on its own; mechanisms like this lead to complications such as dyskinesia. These same mechanisms cause non-motor complications. Dopamine agonists, which mimic dopamine at the receptor, are often used to address apathy and low motivation for this reason. Ultimately, a treatment approach that causes less extreme dopaminergic changes might be ideal in reducing non-motor complications.

Methodology

We conducted a systematic review and meta-analysis. We identified studies examining

the effects of pharmacological treatments on non-motor symptoms in PD. Searches combined terms related to Parkinson's disease medications, specifically levodopa, dopamine agonists, and MAO-B inhibitors, with non-motor outcome aspects including mood, cognition, and sleep.

Source Selection

Studies were identified using sources such as PubMed, ResearchGate, and other scientific databases to access reliable information. Following the database search, studies were screened for eligibility based on title, abstract, and full-text review. The final sample reflected a range of methodological designs, capturing the breadth of available evidence on this topic.

For mood outcomes, Costello et al. (2024) employed a longitudinal observational design, following 412 patients with newly diagnosed Parkinson's disease over five years. Ganjavi and MacDonald (2015) used a within-subject ON/OFF medication-state comparison, enrolling 33 patients with Parkinson's disease alongside 29 healthy controls. Richard et al. (2005) conducted a small, double-blind, randomized, crossover pilot study comparing oral carbidopa/levodopa with continuous levodopa infusion in six patients with idiopathic Parkinson's disease. Hurt et al. (2014) drew on the PROMS-PD dataset to perform a large cross-sectional observational analysis across 500 patients, examining relationships between medication use, mood phenotype, and impulse control behaviors.

For cognitive outcomes, Roy et al. (2018) contributed a systematic review synthesizing findings from 14 studies focused on the effects of antiparkinsonian medications on cognition in patients with mild-to-moderate, non-demented Parkinson's disease.

For sleep outcomes, Kaynak et al. (2005) used a before-and-after treatment design with overnight polysomnography and Multiple Sleep Latency Testing in 15 newly diagnosed patients who had never received antiparkinsonian medication. Razmy et al. (2004) additionally conducted

a prospective polysomnographic study of 80 patients receiving dopamine agonist therapy, using both the Multiple Sleep Latency Test and the Maintenance of Wakefulness Test. Ataide et al. (2014) performed a cross-sectional analysis of 42 patients using the Epworth Sleepiness Scale, the Beck Depression Inventory, and Hoehn and Yahr staging. Frucht et al. (1999) reported a clinical case series of nine patients who experienced sudden sleep episodes while driving.

Finally, for quality-of-life data, Dhar et al. (2025) conducted a cross-sectional hospital-based study of non-motor symptom burden and its relationship to quality of life, and Deuel and Seeberger (2020) provided a narrative review of non-motor symptoms that persist despite standard dopaminergic treatment.

Inclusion Criteria

As we searched for studies examining the effects of Parkinson's medications on non-motor functions, we applied four inclusion criteria. Firstly, we focused on patients who have been diagnosed with idiopathic, or "standard" Parkinson's disease. This established a common baseline when measuring the impact of medication on patients. This also helped to keep results consistent because different disorders can respond to medication differently; side effects were reported in 64.3% of patients with atypical parkinsonism compared with 23.5% of patients with PD (Vasta et al., 2017). Second, we included studies that focus on common Parkinson's medications. These medications include levodopa, dopamine agonists, and MAO-B inhibitors. We specifically included studies of these drugs to understand their impact on non-motor function. Eligible studies had to examine the effects of at least one established antiparkinsonian pharmacotherapy, specifically levodopa or carbidopa/levodopa formulations, dopamine agonists, or MAO-B inhibitors. Third, we included studies that analyzed non-motor symptoms relevant to Parkinson's disease, such as depression, anxiety, cognition, and issues with sleep. Finally, to

ensure the validity of our results, we included recent data, specifically peer-reviewed studies published in the past 20 years. This was done to ensure our findings reflect current clinical understanding and practice, with one exception: Frucht et al. (1999), as it is the original clinical description of dopamine agonist-associated sleep attacks. This data was collected to conduct a meta-analysis and then to answer the research question.

Data Synthesis and Analysis

Following source selection, we conducted a meta-analysis. We analyzed these papers to identify associations between drugs and their effects on non-motor functions. Most of the papers were case studies, ranging from longitudinal to cross-sectional. They primarily studied the impact Parkinson's medications had on patients and their lifestyles.

Given the heterogeneity in study designs and outcome measures across the included literature, we performed a narrative synthesis. Data were extracted and organized by non-motor outcome type, with the present paper focusing on mood, sleep, and cognitive function. Studies were then analyzed for directional consistency, with particular attention to convergent findings across different methodological designs. Any contradictory evidence was noted and contextualized in relation to methodological differences between studies. Associations between specific medication classes and non-motor outcomes were characterized using patterns that emerged across the included literature. Because effect sizes and measurement instruments were not comparable across studies, we report findings as direction of effect rather than magnitude.

Results

Effects on Mood

Mood-related outcomes showed mixed effects across dopaminergic therapies. In a longitudinal observational study of newly diagnosed Parkinson's disease patients, Costello et al.

(2024) found that dopamine agonists were associated with lower motivation symptoms over time, with a medication-by-time interaction of β = -0.06, 95% CI [-0.13, -0.01], p = .039. Dopamine agonists also lowered the odds of clinically significant apathy/anhedonia, OR = 0.68, 95% CI [0.49, 0.94], p = .021. This suggests that dopamine agonists may be more helpful for motivation-related symptoms rather than general depressed mood.

MAO-B inhibitors were more strongly associated with depressive symptoms. Costello et al. (2024) found that MAO-B inhibitor use was associated with lower depression symptoms overall, β = -0.14, 95% CI [-0.27, -0.02], p = .026. MAO-B inhibitors also showed some benefit for motivation symptoms, but this effect was weaker in patients with greater striatal dopaminergic neurodegeneration, OR = 0.28, 95% CI [0.11, 0.73], p = .009. This shows that the effect of MAO-B inhibitors may depend partly on disease progression. Levodopa, by contrast, was not significantly associated with either the motivation or the depression symptom dimension in the same model. These findings from Costello et al. (2024) are summarized in Table 1.

Table 1. Adjusted Mixed-Effects Model Results from Parkinson's Disease Medication and Mood Symptom Dimensions

Medication	Model term	Motivation factor, β (95% CI)	Depression factor, β (95% CI)	Brief interpretation
Dopamine agonists	Drug	0.15 (−0.06 to 0.36)	−0.03 (−0.16 to 0.11)	Dopamine agonists were significantly associated with lower motivation symptoms over time, but not lower depression symptoms.
	Drug × time	**−0.06 (−0.13 to −0.01)***	0.01 (−0.02 to 0.05)	
Levodopa	Drug	−0.15 (−0.35 to 0.05)	0.00 (−0.12 to 0.13)	Levodopa did not show a statistically significant relationship with either motivation or depression factor scores in this model.
	Drug × time	0.04 (−0.02 to 0.09)	0.01 (−0.03 to 0.04)	
MAO-B inhibitors	Drug	−0.08 (−0.29 to 0.12)	**−0.14 (−0.27 to −0.02)***	MAO-B inhibitors were significantly associated with lower depression symptoms overall, but not with a significant longitudinal change over time.
	Drug × time	−0.01 (−0.07 to 0.04)	0.03 (−0.01 to 0.07)	

Note. Adapted from Costello et al. (2024). Values represent β coefficients with 95% confidence intervals from adjusted longitudinal linear mixed-effects models (n = 412). Bolded values indicate statistically significant findings. "Drug" represents the effect of medication use averaged across all time points; "drug × time" represents the longitudinal medication-by-time interaction. COMT inhibitors and amantadine are excluded as they fall outside the scope of the present review.
*$p < .05$.

However, dopaminergic therapy did not show only positive mood effects. In a within-subject ON/OFF medication-state comparison of 33 Parkinson's disease patients and 29 healthy controls, Ganjavi and MacDonald (2015) found that patients had higher anxiety, depression, and apathy scores than controls regardless of medication state. Anxiety scores were significantly higher when patients were ON dopaminergic medication compared to OFF medication, while depression and apathy did not significantly change between ON and OFF states. This suggests that dopaminergic therapy may worsen anxiety in some patients.

Mood effects related to levodopa were also inconsistent. Richard et al. (2005) conducted a small double-blind, randomized crossover pilot study comparing oral carbidopa/levodopa with continuous levodopa infusion in six patients with Parkinson's disease. Four of the six patients showed mood fluctuations, but the direction of improvement differed. Two patients had fewer mood fluctuations during active levodopa infusion, while two had fewer fluctuations during the oral levodopa day. This suggests that levodopa-related mood effects may vary by patient.

Dopaminergic medication was also associated with mood-linked behavioral effects. In a cross-sectional observational analysis of 500 Parkinson's disease patients, Hurt et al. (2014) found that impulse control behavior symptoms were present in 17.8% of patients. Patients with these symptoms had higher total combined levodopa/agonist equivalent intake and were more likely to show an anxious mood phenotype. This suggests that higher combined dopaminergic medication exposure may be related to impulsive behavior and anxiety-related mood patterns.

Table 2. Effects of Parkinson's Disease Pharmacotherapy on Mood

Type/ Aspect	Levodopa	Dopamine Agonists	MAO-B Inhibitors
Depression	*mixed*	*not significant*	*benefit*
Anxiety	*no data*	*harm*	*no data*
Apathy/ Motivation	*no data*	*benefit*	*benefit*

Colors in the table demonstrate direction only, not magnitude. Medication effects on mood are mixed. Dopamine agonists were most associated with improvement in motivation/apathy symptoms, while MAO-B inhibitors were associated with improvement in depression symptoms. However, dopaminergic therapy may also worsen anxiety in some patients, and levodopa-related mood effects may vary by patient.

Effects on Cognition

Cognitive outcomes also showed mixed effects across antiparkinsonian medications. Roy et al. (2018) conducted a systematic review of 14 studies examining the cognitive effects of levodopa, pramipexole, selegiline, and rasagiline in mild-to-moderate, non-demented Parkinson's disease patients. The average methodological quality of the included studies was low, with a mean score of 49.1%, so the findings should be interpreted carefully.

In any case, Levodopa showed both beneficial and harmful cognitive effects. It was associated with benefits on tests of attention, processing speed, and working memory, which the review treated as a single outcome. It was also beneficial for executive function, episodic memory, and verbal fluency. However, levodopa was associated with deleterious effects on a test of cognitive inhibition (Roy et al., 2018). This shows that levodopa does not have one consistent effect on cognition, but instead may help some cognitive domains while worsening others.

Other medications showed more specific cognitive patterns. Pramipexole was associated with worsened episodic memory and impulse control, while selegiline was linked to decline in global cognition over time and poorer concept formation (Roy et al., 2018). In contrast, rasagiline showed possible benefits in working memory and verbal fluency. Overall, these findings suggest that antiparkinsonian medications affect cognition differently depending on the

medication and the specific cognitive domain being measured. These medication-specific cognitive findings are summarized in Table 3.

Table 3. Effects of Parkinson's Disease Pharmacotherapy on Cognition

Domain/ Medication	Levodopa	Pramipexole	Selegiline	Rasagiline
Attention / Processing Speed	*benefit*	*no data*	*no data*	*no data*
Working Memory	*benefit*	*no data*	*no data*	*benefit*
Executive Function	*benefit*	*no data*	*no data*	*no data*
Cognitive Inhibition	*harm*	*no data*	*no data*	*no data*
Episodic Memory	*benefit*	*harm*	*no data*	*no data*
Global Cognition	*no data*	*no data*	*harm*	*no data*
Concept Formation	*no data*	*no data*	*harm*	*no data*
Verbal Fluency	*benefit*	*no data*	*no data*	*benefit*
Impulse Control	*no data*	*harm*	*no data*	*no data*

Based on Roy et al. (2018). Effect direction is summarized across 14 studies; all statistically significant.

The patterns here also overlap with the mood findings: the impulse control effects reported for pramipexole by Roy et al. (2018) parallel the dose-related impulse control behaviors reported by Hurt et al. (2014), which suggests these domains are not necessarily separable.

Effects on Sleep

Sleep is one of the non-motor functions negatively affected by Parkinson's disease and dopaminergic therapy such as levodopa and dopamine agonists. Sleep disturbance can take various forms, including daytime sleepiness, poor overall sleep quality, and sleep disorders.

A correlational study conducted on 15 patients with Parkinson's disease, all untreated and later treated with dopaminergic therapy, demonstrated that daytime sleepiness emerges at the start of treatment (Kaynak et al., 2005). It was measured through the Multiple Sleep Latency Test

(MSLT), which indicates that normal sleep latency is 10 to 20 minutes, and a score of 8 minutes or less with two or more Sleep-Onset Rapid Eye Movement (SOREM) periods suggests narcolepsy when no other confounding variables are present. The mean MSLT score decreased significantly after dopaminergic treatments, from 13.6 minutes to 8.1 minutes, indicating excessive daytime sleepiness. Some patients also showed two or more SOREM periods, a feature commonly associated with narcolepsy. Although results may differ between patients, this indicates that sleep disturbance caused by dopaminergic therapy can be severe, presenting symptoms consistent with sleep disorders such as narcolepsy.

Although dopamine agonists and levodopa (L-DOPA) are both dopaminergic therapies commonly used in Parkinson's disease patients, excessive daytime sleepiness (EDS) was more directly associated with levodopa dosage. In another cross-sectional study of 42 patients with Parkinson's disease, patients without EDS had a mean levodopa dose of 366.7 mg. In contrast, those with EDS had approximately 460.4 mg, a statistically significant difference ($p = 0.038$) (Ataide et al., 2014). By contrast, the combination of levodopa with the dopamine agonist pramipexole did not reveal a significant association with EDS in the same sample. Ataide et al. (2014) also reported that patients with higher depression scores recorded lower Epworth Sleepiness Scale (ESS) values than other patients ($p = .03$), which raises the possibility that self-report instruments do not capture sleepiness equally well across mood states.

Table 4. Descriptive statistics (n=42)

Measure	Mean ± SD
Age (years)	61.2 ± 11.3
Gender (masculine/feminine)	25/17*
Duration of disease (years)	4.96 ± 3.3
Hoehn and Yahr modified stage	2.1 ± 0.98
Mini-Mental State Examination	26.7 ± 2.6
Epworth sleepiness scale	7.5 ± 4.7
Beck depression inventory	18.7 ± 10.7
Levodopa dosage (mg)	393.45 ± 261.4
Levodopa dosage equivalents (mg)	441.3 ± 272.5

Table 5. Comparison of variable scores according to excessive daytime sleepiness

	Epworth < 10 (n = 30)	Epworth ≥ 10 (n = 12)	P (value)
	Mean ± SD	Mean ± SD	
Age (years)	61.5 ± 11.8	60.5 ± 10.4	0.327
Gender (male/female)	11/19*	9/3*	0.594
Duration of disease (years)	5.05 ± 3.1	4.75 ± 3.9	0.157
Hoehn and Yahr modified version	2.1 ± 1.0	2.1 ± 1.0	0.428
Mini-Mental State Examination	26.6 ± 2.8	27.1 ± 2.2	0.089
Beck depression inventory	20.6 ± 10.9	13.8 ± 9.1	0.056
Levodopa dosage (mg)	366.7 ± 228.0	460.4 ± 332.25	0.038
Levodopa dosage equivalents (mg)	410.8 ± 235.1	517.6 ± 348.2	0.46

A larger polysomnographic study of 80 patients with Parkinson's disease receiving dopaminergic therapy reached a similar conclusion about dose. Mean MSLT scores did not differ between patients taking pramipexole, ropinirole, or ergot agonists such as bromocriptine and pergolide, but high Levodopa Dosage Equivalent (LDE) greater than 867.5 mg was the main risk factor associated with pathological daytime sleep latency, OR = 4.2, 95% CI [1.3, 13.7] (Razmy et al., 2004). Fifteen of the 80 patients, or 18.8%, met criteria for pathological daytime sleep latency. ESS scores were not related to objectively measured impairment in that sample, which reinforces the concern raised by Ataide et al. (2014) that subjective reporting alone may understate the problem. Collectively, these findings indicate that total dopaminergic dosage, rather than the specific agonist used, is the stronger contributor to sleep disturbance.

Sleep disturbance in this population is not limited to gradual sleepiness. Frucht et al. (1999) described nine patients with Parkinson's disease, eight taking pramipexole and one taking ropinirole, who experienced sudden irresistible sleep episodes, also called sleep attacks, while driving. Five of the nine experienced no warning before falling asleep, and the attacks ceased when the drugs were stopped. Because patients in the polysomnographic studies were poor judges of their own sleepiness, this combination of findings has direct safety implications.

This overall reveals that not all dopaminergic therapies carry the same risk of EDS and that dopaminergic dosage is a significant contributor to sleep disturbance.

Aggregated Effect on Quality of Life

When considered in aggregate, these findings demonstrate that dopaminergic therapy for Parkinson's disease brings significant non-motor consequences that reduce quality of life. In a cross-sectional hospital-based study, Dhar et al. (2025) reported that non-motor symptoms affect as many as 90% of patients over the course of the illness and that the sleep/fatigue and mood/cognition domains were significantly correlated with one another and with disease duration. Deuel and Seeberger (2020) similarly noted that anxiety and depression commonly persist in patients whose motor symptoms are adequately controlled by dopaminergic therapy, which is one reason clinical interest in complementary and non-dopaminergic approaches has grown. These findings indicate that treatment success defined by motor goals alone can leave a considerable portion of patient burden unaddressed.

Discussion

This review examined how levodopa, dopamine agonists, and MAO-B inhibitors affect non-motor symptoms in patients with Parkinson's disease. While all three drug classes effectively manage motor symptoms, their effects on mood, sleep, and cognition were inconsistent and at times contradictory. Levodopa and rasagiline showed some benefit for mood and specific cognitive domains, such as attention and memory. At the same time, pramipexole and selegiline were associated with worsening of impulse control and global cognition. Mood symptoms such as depression and anxiety often persisted even while patients were on medication, and sleep frequently worsened with treatment, with higher levodopa doses predicting

excessive daytime sleepiness and dopamine agonists linked to sudden sleep attacks. Together, these findings reinforce that non-motor symptoms remain a major driver of reduced quality of life, even when motor symptoms are well controlled.

There are two main patterns to consider. First, dose is more relevant than drug class, as was clearest in the sleep literature, where agonist type was not independently associated with sleepiness but total levodopa-equivalent dose was. The same pattern emerged in impulse control findings, where combined dopaminergic intake was distinguished from unaffected patients. Second, patients are often poor reporters of their own non-motor state, so it appears that subjective sleepiness scales failed to identify patients with objective impairment in two separate samples, and depressed mood appeared to alter self-reported sleepiness. This has practical consequences for how non-motor symptoms are screened in clinics.

Limitations & Evaluation

Several limitations should temper the interpretation of these results. Few studies directly compare multiple medications across multiple non-motor domains, and outcome measurement varied widely, with different scales used for mood, cognition, and sleep. Sample sizes ranged from six to 500, and several of the strongest directional claims rested on small samples. Also, the cognitive findings derive from a single systematic review whose included studies were rated low in methodological quality, with a mean score of 49.1%. Most designs were additionally observational, so medication effects cannot be separated from disease severity, since patients on higher doses generally have more advanced disease.

Moreover, many studies were short-term, leaving long-term effects understudied. Also, patient responses varied considerably depending on disease progression and individual

differences. These inconsistencies reflect the fact that non-motor symptoms are shaped by multiple neurotransmitter systems, which limits how much dopaminergic therapy alone can do.

Conclusion

These findings demonstrate that dopaminergic therapy for Parkinson's disease has significant non-motor consequences that reduce quality of life. Although motor symptoms are well controlled with dopaminergic therapy, the effects on non-motor functions, such as mood, sleep, and cognition, are bidirectional and complex. Considering the effects of different types of dopaminergic therapy on mood, dopamine agonists are associated with reduced apathy and motivational symptoms. In contrast, MAO-B inhibitors are associated with lower depression scores. Anxiety is higher in patients in ON states, suggesting that mood effects are bidirectional, meaning it cannot be uniformly beneficial. Dopaminergic therapy on sleep disturbance shows that not all dopaminergic therapies carry the same risk of EDS and that dosage is a significant contributor to sleep disturbance. As for cognition, while levopopa and rasagiline show significant benefits in attention and memory, pramipexole is associated with worsened impulse control, and selegiline is associated with worsened global cognition. These findings highlight that effective management of Parkinson's requires attention beyond motor symptoms, as the non-motor consequences of therapy also affect patients' daily functioning, including overall quality of life.

Future Directions

Future research should move away from studying single drugs or single symptoms in isolation and instead compare medications across multiple non-motor domains simultaneously, using longitudinal designs that capture long-term tradeoffs. Studies that separate dose effects from disease-severity effects would be particularly valuable, given how consistently dose becomes the operative variable in this review. There is also a strong case for developing

non-dopaminergic therapies targeting the serotonergic, noradrenergic, and cholinergic systems involved in mood, sleep, and cognition, along with adjunctive strategies such as SSRIs or CBT for depression and anxiety, melatonin and sleep hygiene for sleep disturbances, and cholinesterase inhibitors for cognitive decline. Trials that use non-motor outcomes as primary goals rather than secondary ones would help close the evidence gap, particularly for sleep. Clinicians should also raise awareness of underrecognized risks like sleep attacks, which patients often underestimate. Above all, the field would benefit from a stronger emphasis on patient-centered outcomes, particularly overall quality of life, rather than relying so heavily on motor goals to define treatment success.

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