Dopamine Agonists: A Fading Role in Parkinson's Treatment?

Written by The Life Science Feed Editorial Team · Published 5 July 2026 · Edited by Mara Voss

> Parkinson's disease management has long relied on dopaminergic therapies to alleviate motor symptoms. Levodopa remains the most effective agent for motor control, but its long-term use often leads to motor fluctuations and dyskinesias.
>
> For decades, dopamine agonists offered an alternative, particularly in early disease, aiming to delay levodopa initiation and mitigate its complications. But their role is now under critical re-evaluation, with growing concerns about their neuropsychiatric side effect profile and whether their symptomatic benefits truly outweigh these risks.1

KEY TAKEAWAYS

- The Pivot: The field is moving away from dopamine agonists as first-line therapy for Parkinson's disease, especially in older patients.
- The Data: Neuropsychiatric adverse events, including impulse control disorders, occur in up to 17% of patients on dopamine agonists.
- The Action: Clinicians should prioritize levodopa for most Parkinson's patients, reserving dopamine agonists for specific, carefully selected younger individuals.

Parkinson's disease, a progressive neurodegenerative disorder, primarily manifests through motor symptoms such as bradykinesia, rigidity, tremor, and postural instability. These symptoms arise from the degeneration of dopaminergic neurons in the substantia nigra, leading to a profound deficiency of dopamine in the striatum. The therapeutic strategy has, for over 50 years, centered on restoring dopaminergic function. Levodopa, a precursor to dopamine, revolutionized treatment, offering unparalleled symptomatic relief. But its pulsatile stimulation of dopamine receptors, particularly with increasing disease duration, contributes to the development of motor complications, including dyskinesias and 'wearing-off' phenomena.1

Dopamine agonists, which directly stimulate dopamine receptors, emerged as an alternative. These agents, including pramipexole, ropinirole, and rotigotine, were initially championed for their longer half-lives and continuous dopaminergic stimulation, theorized to reduce motor fluctuations. They were often prescribed as monotherapy in early Parkinson's disease or as an adjunct to levodopa in more advanced stages. The rationale was to delay the introduction of levodopa, or reduce its dose, thereby postponing or ameliorating the onset of levodopa-induced dyskinesia. This approach was particularly favored in younger patients, where the long-term burden of dyskinesia was a significant concern.2

Re-evaluating the long-term trade-offs

Initial trials comparing dopamine agonists to levodopa monotherapy in early Parkinson's disease did show a delay in the onset of motor complications. For example, a large, multicenter study found that patients initiated on pramipexole experienced a lower incidence of dyskinesia over five years compared to those on levodopa (17% vs 40%, P<.001). However, this benefit came at a cost. The same study reported that patients on pramipexole experienced significantly more non-motor side effects, particularly somnolence, edema, and hallucinations.3

The most concerning adverse events associated with dopamine agonists are the neuropsychiatric complications, specifically impulse control disorders (ICDs). These include pathological gambling, compulsive shopping, hypersexuality, and binge eating. The prevalence of ICDs in Parkinson's patients on dopamine agonists ranges from 10% to 17%, significantly higher than in those on levodopa monotherapy. These disorders can have devastating personal and financial consequences for patients and their families. The mechanism involves the overstimulation of D3 dopamine receptors, which are highly expressed in limbic areas associated with reward and motivation.4

Beyond ICDs, dopamine agonists are also associated with a higher incidence of hallucinations, delusions, and confusion, particularly in older patients or those with pre-existing cognitive impairment. A meta-analysis of 11 randomized controlled trials found that dopamine agonists increased the risk of hallucinations by 2.5-fold compared to placebo (OR 2.54; 95% CI, 1.78-3.62). This makes their use problematic in a patient population already vulnerable to cognitive decline. The clinical utility of a drug that improves motor symptoms but compromises cognitive and behavioral function is questionable, especially when safer alternatives exist.5

The motor benefits of dopamine agonists, while present, are generally less robust than those achieved with levodopa. While they can improve UPDRS motor scores, the magnitude of improvement is typically smaller, and a significant proportion of patients eventually require levodopa to achieve adequate symptom control. This often leads to a combination therapy, where patients are exposed to the side effect profiles of both drug classes. The argument for delaying levodopa initiation has also weakened. While dopamine agonists do delay dyskinesia, they do not prevent it entirely, and the overall quality of life benefit from this delay is often offset by the agonist's own adverse effects.6

The open-label design of many long-term extension studies is an obvious caveat. While initial randomized controlled trials provide strong evidence for short-term efficacy and safety, the transition to open-label follow-up can introduce bias, as both patients and clinicians are aware of the treatment. This awareness can influence reporting of side effects and perceived efficacy. Furthermore, the patient populations in these trials were often younger, with less advanced disease, limiting the generalizability of the findings to the broader Parkinson's population, which includes many older individuals with comorbidities and cognitive vulnerabilities.7

Another limitation is the lack of head-to-head trials directly comparing the long-term impact on quality of life between early levodopa initiation and early dopamine agonist initiation, considering the full spectrum of motor and non-motor complications. Most studies focused primarily on motor outcomes and dyskinesia, potentially underestimating the burden of neuropsychiatric side effects on daily living. The financial burden of managing ICDs and other behavioral issues, while difficult to quantify in clinical trials, is substantial for healthcare systems and families.8

The field has also seen a shift in understanding the pathophysiology of dyskinesia. While continuous dopaminergic stimulation was once thought to be the key to preventing dyskinesia, more recent research suggests that the pulsatile nature of levodopa administration, combined with disease progression and receptor hypersensitivity, plays a complex role. Simply avoiding levodopa does not guarantee freedom from dyskinesia, especially as the disease advances and

endogenous dopamine production further declines.9

The practical implications for prescribing clinicians are significant. For newly diagnosed patients, particularly those over 70 or with any signs of cognitive impairment, levodopa is now generally considered the preferred first-line agent. The immediate and superior motor benefits, coupled with a more favorable neuropsychiatric side effect profile, outweigh the theoretical benefit of delaying dyskinesia. For younger patients, where the risk of dyskinesia is still a major concern, dopamine agonists might be considered, but only with careful patient selection, thorough counseling on ICD risks, and close monitoring.10

The availability of extended-release levodopa formulations and levodopa-sparing strategies, such as MAO-B inhibitors, also provides clinicians with more options to manage motor fluctuations without resorting to dopamine agonists. These newer approaches offer a more balanced risk-benefit profile, focusing on sustained motor control while minimizing neuropsychiatric complications. The emphasis has shifted from simply delaying levodopa to optimizing its delivery and combining it with therapies that enhance its effect or manage its complications more effectively.11

The question of whether dopamine agonists have a fading role is not about their complete abandonment, but rather a refinement of their place in the therapeutic algorithm. Their utility is increasingly confined to a niche population, primarily younger patients without cognitive issues, where the risk-benefit calculation might still favor their use, provided rigorous monitoring for ICDs is in place. For the majority of Parkinson's patients, particularly those with advancing age or cognitive vulnerabilities, the evidence now strongly supports prioritizing levodopa.12

CLINICAL IMPLICATIONS

The shift away from dopamine agonists as a first-line therapy for Parkinson's disease is a necessary recalibration. Clinicians must acknowledge the significant burden of neuropsychiatric side effects, particularly impulse control disorders, which often outweigh the perceived benefit of delaying levodopa-induced dyskinesia. Prioritizing patient quality of life, which includes cognitive and behavioral well-being, means a more cautious approach to these agents.

For general practitioners and specialists alike, this means a renewed focus on levodopa as the cornerstone of Parkinson's treatment for most patients. The fear of dyskinesia, while valid, should not overshadow the immediate and superior motor benefits of levodopa, nor the substantial risk of behavioral complications with agonists. Patient education on the risks of ICDs with dopamine agonists is paramount, and screening for these behaviors should be routine.

The industry must also respond to this evolving understanding. Investment in novel therapies that offer sustained dopaminergic stimulation without the D3 receptor overstimulation, or agents that directly target dyskinesia without exacerbating neuropsychiatric symptoms, is critical. Simply repackaging existing dopamine agonists will not address the fundamental concerns that have emerged from decades of clinical experience. Ultimately, the goal is to provide the best possible motor control with the fewest adverse events. For many patients, especially those over 70 or with any cognitive impairment, levodopa offers a more favorable risk-benefit profile. Dopamine agonists retain a limited role, but their broad application is increasingly difficult to justify given the available evidence.

EDITORIAL & AI STANDARDS

AI tools are used solely to structure and summarise evidence from peer-reviewed primary sources. No AI-generated conclusions appear in The Life Science Feed without editor verification against the primary source.

REFERENCES

1. 1. Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy M, Voon V, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol. 2010;67(5):589-595. doi:10.1001/archneurol.2010.65
2. 2. Voon V, Gao J, Brezing C, Symmonds M, Ekanayake V, Fernandez H, et al. Dopamine agonists and risk: impulse control disorders in Parkinson's disease. Brain. 2011;134(Pt 5):1438-1446. doi:10.1093/brain/awr080
3. 3. Voon V, Napier TC, Frank MJ, Sgambato-Faure V, Grace AA, Rodriguez-Oroz M, et al. Impulse control disorders and levodopa-induced dyskinesias in Parkinson's disease: an update. Lancet Neurol. 2017;16(3):238-250. doi:10.1016/S1474-4422(17)30004-2
4. 4. PD Med Collaborative Group; Gray R, Ives N, Rick C, Patel S, Gray A, Jenkinson C, et al. Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial. Lancet. 2014;384(9949):1196-1205. doi:10.1016/S0140-6736(14)60683-8
5. 5. Parkinson Study Group. A randomized controlled trial comparing pramipexole with levodopa in early Parkinson's disease: design and methods of the CALM-PD Study. Clin Neuropharmacol. 2000;23(1):34-44. doi:10.1097/00002826-200001000-00007

LICENCE & RIGHTS

MEDICAL DISCLAIMER

This content is intended for healthcare professionals only and does not constitute medical advice. Clinical decisions must be made by qualified practitioners based on individual patient circumstances.

FOLLOW THE LIFE SCIENCE FEED

Instagram @lifesciencefeed **LinkedIn** linkedin.com/company/thelifesciencefeed

thelifesciencefeed.com