

The road towards faster development of novel pharmacotherapies for persons with Parkinson's disease

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Editorial

Parkinson's disease (PD) remains one of the most challenging areas in neurotherapeutics, with major progress in symptomatic treatment but persistent failure to deliver effective disease-modifying therapies. However, we are entering a new phase in therapeutic development for PD. Clinical trials are now targeting mechanisms closer to the presumed pathobiology of the disease, such as alpha-synuclein pathology or specific genetic pathways. Furthermore, the imminent arrival of blood tests for diagnostic biomarkers will allow us to identify individuals at a much earlier disease phase when the underlying disease pathology is not yet far advanced, significantly expanding the pool of candidates for early interventions aimed at delaying disease progression.

This special issue of the *Journal of Parkinson's Disease*, entitled "Roads towards a faster development of new pharmacotherapies for Parkinson's disease", brings together a set of manuscripts that collectively map the field's most important opportunities and bottlenecks, from patient priorities and therapeutic pipelines to trial design, biomarkers, regulators, and target-specific treatment needs. The common message across these contributions is that faster progress will require more than incremental refinement of existing strategies. It will depend on better alignment between patient needs, mechanistic insights, trial methodology, regulatory pathways, and the practical realities of drug development for a disease characterized by substantial clinical and pathobiological heterogeneity.

The opening contribution by McFarthing et al.¹ emphasizes an essential but sometimes underappreciated point: any successful therapeutic agenda must begin with the needs and expectations of people with PD. Patients are not primarily interested in the taxonomy of drug mechanisms – they want treatments that improve their quality of life, simplify care and, ideally, slow or halt progression. The manuscript reminds us that the medicines people with PD desire must be judged not only by efficacy, but also by convenience, affordability, and honest communication that sustains hope without inflating expectations.

This patient-centered perspective sets the stage for the next paper, which examines gaps in the therapeutic pipeline targeting disease pathobiology. Stefanis et al.² highlight a paradox familiar to the field: despite an increasingly sophisticated understanding of PD biology, there is still no approved disease-modifying therapy. The manuscript underscores the need to strengthen the translational chain from biology to clinical trials by improving biomarkers, models,

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and delivery strategies, while also considering complementary approaches that may advance more readily into human studies.

A complementary theme is developed in the paper by Poewe et al.,³ which reviews unmet needs in the pharmacological management of motor symptoms. Although levodopa and related dopaminergic strategies remain the backbone of care, important therapeutic gaps persist, especially in more advanced disease stages. Poorly responsive tremor, motor fluctuations, gait and balance impairment, and problems with posture, speech, and swallowing remain difficult to treat, reinforcing the need for new targets, improved delivery systems, and combination approaches tailored to changing clinical stages.

Machado and colleagues⁴ performed a cross-sectional analysis of registered PD trials and stratified them according to the types of pharmacological agents and targets. They found that the clinical trial space is dominated by those focusing on dopaminergic approaches, and those focusing on targeting alpha-synuclein. Their findings suggest that despite an increase in the landscape of PD trials, progress has been essentially limited to incremental improvements in dopaminergic therapies, suggesting additional effort needs to be put into the way we think about drug development in PD.

The manuscript by Postuma et al.⁵ shifts the focus upstream, to prevention trials. This is a critical frontier because intervention timing may determine whether a therapy can genuinely alter the course of PD. The paper argues that the field must move beyond conventional clinical scales and toward biomarker-informed strategies that identify individuals at the highest risk, before extensive neurodegeneration has occurred. It also stresses the importance of biologically grounded stratification, sensitive endpoints, and early stakeholder engagement to make prevention trials both feasible and ethical.

Falup-Pecurariu and colleagues⁶ then address sleep disorders, another major non-motor domain that is highly prevalent, heterogeneous, and clinically consequential. Their review highlights the breadth of sleep problems in PD, including insomnia, REM sleep behavior disorder, restless legs syndrome, daytime sleepiness, and sleep-related breathing disorders. The paper emphasizes that current therapeutic options remain limited and that deeper pathophysiological insight is needed to enable more personalized interventions for this important symptom complex.

The review by Pontone et al.,⁷ on psychiatric symptoms, highlights a domain where the field still lacks treatments designed specifically for PD. Psychiatric symptoms are common, can emerge early, and interact in complex ways with motor features and their therapies. The manuscript raises a central question: should the field continue adapting general psychiatric drugs for use in PD, or should it pursue medicines developed specifically for the biology and clinical context of PD? That question captures, in many ways, the broader spirit of this special issue.

The contribution by Abdelnour et al.⁸ turns to cognitive impairment, one of the most disabling non-motor

manifestations of PD. With rivastigmine still the only approved treatment for Parkinson's disease dementia (PDD) and no approved therapy for mild cognitive impairment in PD, the paper identifies a major unmet need. It argues persuasively that progress will depend on better outcome measures, longer and more sensitive trials, and the integration of biomarkers, digital assessments, and inclusive recruitment strategies capable of capturing patients who are often underrepresented in conventional studies.

Meinert and colleagues⁹ extend this idea by focusing on digital approaches and artificial intelligence. Their review captures how digital technologies are increasingly being used to improve target identification, candidate selection, dose optimization, and remote data capture. The manuscript also notes that most innovation has occurred before clinical trials, leaving a need to better integrate digital tools into the actual conduct of clinical studies. In doing so, it points toward a future in which AI-enabled design and monitoring could make trials more adaptive, efficient, and informative.

Rosa and colleagues¹⁰ then examine the regulatory side of the equation. Their paper makes clear that the development bottleneck is not solely scientific – it is also procedural and structural. Regulatory agencies already offer advice and facilitation mechanisms, but more effective use of these pathways may be necessary to accelerate approval of new medicines. The manuscript is a timely reminder that progress in PD therapeutics depends on stronger interaction between regulators, developers, and researchers throughout the drug-development process.

Taken together, the papers in this special issue show that the road toward faster development of new pharmacotherapies for PD must be multi-lane rather than single lane. It will require a deeper pathobiological understanding, better target and patient selection, stronger biomarkers, more sensitive and inclusive trial designs, clearer regulatory facilitation, and a sustained focus on outcomes that matter to patients. Progress will not come from any one breakthrough alone, but from a coordinated effort to reduce friction at every stage of the therapeutic pipeline.

We hope that these articles will stimulate further work, sharpen research priorities, and accelerate the development of therapies that are not only scientifically compelling, but also clinically meaningful for people living with PD.

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