



Review Article

Research Trends and Hotspots in Levodopa-induced Dyskinesia: A Bibliometric Analysis (2015-2024)

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Abstract

Levodopa is a core therapeutic agent for Parkinson's disease (PD), while its long-term administration often leads to levodopa-induced dyskinesia (LID), which significantly compromises patients' quality of life. This study utilizes bibliometric analysis to examine research trends in LID over the past decade, with the aim of identifying key research hotspots and prospective directions in the field. Relevant publications published between 2015 and 2024 were retrieved from the Web of Science and PubMed databases. A total of 691 articles were ultimately included for systematic analysis. Visual analytic techniques were applied using VOSviewer and CiteSpace to examine publication trends, contributions by countries and institutions, author collaboration networks, and keyword clustering. The annual number of publications in LID research exhibited a declining trend over the study period, with a peak in 2015. The United States and institution CNRS (Centre National de la Recherche Scientifique) contributed most significantly. Movement Disorders was the leading journal in both publication volume (54 articles) and citations (2,369). Author Huot P. was the most prolific (25 articles). Keyword analysis identified core themes encompassing "disease-drug-complication-intervention-model." The knowledge structure developed around key clusters: disease models and Parkinson Disease/Drug Therapy. Trend analysis revealed a move from retrospective etiology to refined safety assessments and mechanism-driven interventions. This study outlines the global research landscape and developmental trends in LID, thereby providing a theoretical foundation for future investigations into non-invasive brain stimulation, precision medicine, and novel drug therapies. Further research should emphasize early LID prediction, targeted treatments, and multidisciplinary management.

Keywords

Parkinson's Disease, Levodopa-induced Dyskinesia, Bibliometric Analysis, Hotspots, VOSviewer, CiteSpace

1. Introduction

Parkinson's disease (PD) ranks as the second most common progressive neurodegenerative disorder after Alzheimer's disease, with a global prevalence estimated at 1.51 per 1,000 people [1]. Pathologically, the disease is characterized by the progressive loss of dopaminergic neurons in the substantia nigra

pars compacta and the abnormal intracellular accumulation of Lewy bodies.

Levodopa (L-3,4-dihydroxyphenylalanine), a metabolic precursor of dopamine, remains the cornerstone of PD pharmacotherapy. When co-administered with a peripheral decarboxylase inhibitor

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Received: 25 January 2026; Accepted: 12 February 2026; Published: 27 February 2026



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such as carbidopa, it effectively restores striatal dopamine levels. During early treatment stages, levodopa typically provides near-complete relief from core motor symptoms, including tremor, rigidity, and bradykinesia [2].

However, long-term levodopa therapy often leads to motor complications. These include the "wearing-off" phenomenon—the re-emergence of motor and non-motor symptoms as the duration of drug effect shortens—and levodopa-induced dyskinesia (LID). Importantly, dyskinesia results primarily from pharmacodynamic sensitization and functional drug overdose, rather than from inadequately controlled PD symptoms or diminished drug efficacy. Given that LID represents a major clinical challenge in the long-term management of PD, it will be the primary focus of this paper.

2. Methods

2.1. Data Collection

All data were obtained from the Web of Science Core Collection (WoSCC) and PubMed databases, which are internationally recognized authoritative academic repositories. The Web of Science Core Collection search formula was configured as follows: ((AK=("Levodopa"OR "3-Hydroxy-L-tyrosine" OR "Dopaflex" OR "Dopar" OR "L-3, 4-Dihydroxyphenylalanine" OR "L-Dopa" OR "Larodopa" OR "Levopa" OR "Levodopa-induced")) AND AK=("Dyskinesias"OR"Abnormal Movements"OR "Asterixis"OR "Ballismus"OR "Hemiballism"OR "Hemiballismus"OR "Involuntary Movements"OR "Lingual-Facial-Buccal Dyskinesia" OR "Linguofacial Dyskinesia"OR "Oral Dyskinesia"OR "Oral-Facial Dyskinesia"OR "Orofacial Dyskinesia"OR "Tardive Oral Dyskinesia" OR "Dyskinesia")) AND PY=(2015-2024). The following search strategy for PubMed database was used: (((("Levodopa"[Majr] AND ("Dyskinesias"[Majr])) OR (((((((Levodopa[MeSH Terms] OR (3-Hydroxy-L-tyrosine[MeSH Terms])) OR (Dopaflex[MeSH Terms])) OR (Dopar[MeSH Terms])) OR (L-3, 4-Dihydroxyphenylalanine[MeSH Terms])) OR (L-Dopa[MeSH Terms])) OR (Larodopa[MeSH Terms])) OR (Levopa[MeSH Terms])) AND (((((((Dyskinesias[MeSH Terms] OR (Abnormal Movements[MeSH Terms])) OR (Asterixis[MeSH Terms])) OR (Ballismus[MeSH Terms])) OR (Hemiballism[MeSH Terms])) OR (Hemiballismus[MeSH Terms])) OR (Involuntary Movements[MeSH Terms])) OR (Lingual-Facial-Buccal Dyskinesia[MeSH Terms])) OR (Linguofacial Dyskinesia[MeSH Terms])) OR (Oral Dyskinesia[MeSH Terms])) OR (Oral-Facial Dyskinesia[MeSH Terms])) OR (Orofacial Dyskinesia[MeSH Terms])) OR (Tardive Oral Dyskinesia[MeSH Terms]))).

This study systematically retrieved English-language literature published between January 1, 2015, and December 31, 2024. The search was conducted on April 10, 2025, to ensure inclusion of any 2024 publications with delayed database indexing. The Web of Science Core Collection (WoSCC) was

used to screen research articles and review articles, while PubMed was searched for original articles, clinical studies, reviews, and systematic reviews. In accordance with bibliometric research standards, non-research literature—including conference proceedings, edited materials, book chapters, preprints, academic book reviews, and conference abstracts—was excluded. An exact match search using author keywords in Web of Science yielded 549 valid records, and a MeSH term search in PubMed returned 646 valid records. Duplicates were identified and removed based on Digital Object Identifiers (DOIs) and article titles; records without DOIs were manually compared using title, first author, and publication year. This process resulted in a consolidated dataset of 691 unique publications. The resulting standardized RIS dataset was subsequently analyzed (Figure 1).

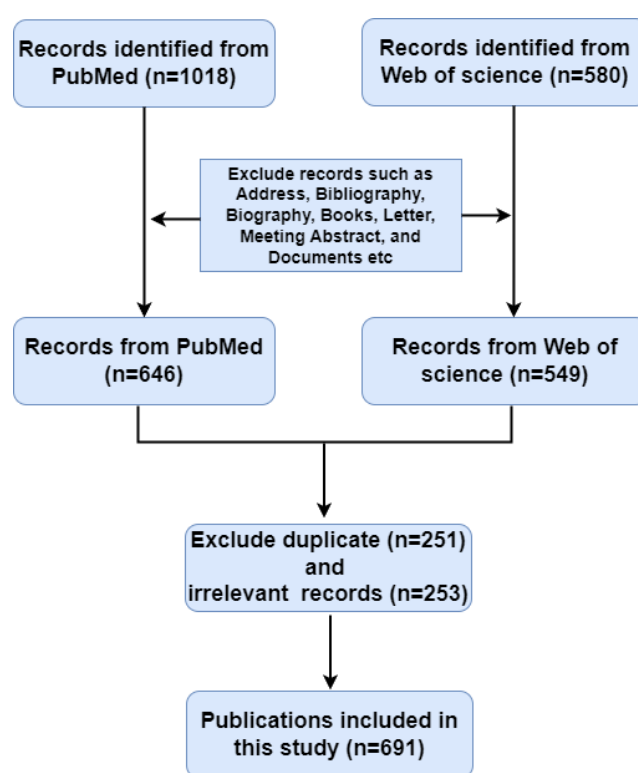


Figure 1. PRISMA flowchart of study selection for research on levodopa-induced dyskinesia. A total of 1,018 records were retrieved from PubMed and 580 from Web of Science. After deduplication by End-Note and exclusion of irrelevant studies, 691 publications were included for final analysis.

2.2. Data Analysis

After completing data collection, we first excluded records unrelated to the research topic and systematically corrected spelling errors in the text. The standardized research dataset was then imported into two professional bibliometric tools—VOSviewer 1.6.20 [3] and CiteSpace 6.1.4 [4]—for in-depth analysis. VOSviewer was employed for visualizing collaborative and co-citation networks, covering countries, institutions,

authors, journals, references, and keywords. In contrast, CiteSpace was dedicated to prospective analyses, including the detection of citation bursts, dual-overlay journal mapping, and keyword clustering combined with timeline analysis.

3. Results

3.1. Annual Publication Volume and Trend Analysis

The number of publications in each period reflects the trend of research in the field. As shown in Figure 2, the development can be divided into three main phases:

Phase I: 2015–2017 commenced with a zenith of 99 publications in 2015, highlighted by a pivotal study conducted by Huot et al. from the University of Toronto, published in *Neuropharmacology*. Employing a non-human primate model, the researchers established that the highly selective 5-HT1A full agonist F15599 markedly alleviated LID without compromising overall motor function, thereby offering essential preclinical validation for forthcoming clinical trials. However, the number of publications experienced a declining trend in the

subsequent years (76 in 2016, 53 in 2017), likely indicative of a phase of relative research saturation and redistribution of resources following the conclusion of several significant projects.

Phase II: 2018–2020 was characterized by variable yet recovering publication outputs, culminating in a resurgence to 97 articles in 2018. This revival was probably propelled by novel methodological innovations and the emergence of new research avenues in LID. After a slight decrease to 71 papers in 2019, output rebounded to 73 papers in 2020, likely due to a strategic shift prioritizing quality over quantity. One possible explanation is that the evolution of remote collaboration models amid the global pandemic, coupled with a renewed focus on neuroscience research to some extent, may have contributed positively to this trend.

Phase III: 2021–2024 witnessed a consistent trend of decline in annual publications, tapering from 65 in 2021 to 45 in 2024. This pattern suggests a maturation of the field, with research becoming increasingly specialized and resources being channeled more towards long-term, interdisciplinary initiatives rather than short-term yield. The emphasis may have transitioned to synthesizing existing knowledge and delving into novel, underexplored domains within LID research.

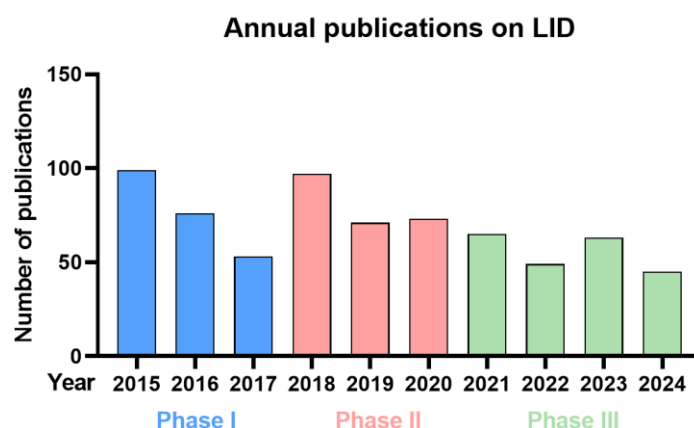


Figure 2. Annual publication volume on Levodopa-Induced Dyskinesia research. The chart shows publication trends across three-time phases: 2015–2017 (Phase I), 2018–2020 (Phase II), and 2021–2024 (Phase III).

3.2. Analysis of Countries and Organizations

The volume of publications and the structure of national collaboration networks offer initial perspectives on each country's position and role in scholarly output and research cooperation within this domain (Figure 3, Table 1). Publication counts were determined based on the corresponding author's country. If the corresponding author has multiple countries of affiliation, we selected the country where their primary affiliation is located. When authors of a paper come from multiple countries, in country-level statistics we employ a full-count method: whenever a country is represented, its count is incre-

mented by one. Betweenness centrality reflects a node's capacity to connect disparate parts of the network; a high value indicates that the node exerts considerable influence over information flow and collaboration within the network. The United States (USA) leads in both publication volume and betweenness centrality. China ranks second in terms of publication count and fifth in betweenness centrality, while Italy places third in both betweenness centrality and in publication volume. In Figure 3, several nodes with pink outer rings exhibit betweenness centrality values exceeding 0.05, signaling notably high mediation potential. As shown in Table 1, USA (0.50) demonstrates the strongest central influence. These insights reveal strategic opportunities for enhancing future international research collaboration.

CiteSpace v. 5.4.R1 (64-bit) Advanced
February 11, 2026, 10:47:05 AM CST
VQS: C:\Users\user\Desktop\CiteSpace\data
Timespan: 2015-2024 (Slice Length=1)
Selection Criteria: g-index (k=25), LRF=2.5, L/N=10, LBY=5, a=1.0
Network: N=341, E=792 (Density=0.0137)
Largest CCs: 274 (80%)
Nodes Labeled: 1.0%
Pruning: None
Excluded:

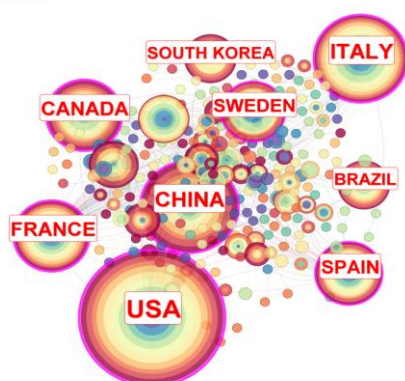


Figure 3. Global research network for Levodopa-Induced Dyskinesia. CiteSpace was used to map country-level collaborations based on co-authored publications from 2015 to 2024. The size of each node reflects the national publication output, and connections represent collaboration strength.

Table 1. Top 10 countries with the most publications.

Rank	Country	Number of articles	Betweenness Centrality
1	USA	218	0.50
2	CHINA	99	0.21
3	ITALY	92	0.29

Table 2. Top 5 organizations with the most publications.

Rank	Organizations	Country	Number of articles
1	CNRS (Centre National de la Recherche Scientifique)	France	49
2	Lund University	Sweden	33
3	University of Bordeaux	France	29
4	McGill University	Canada	26
5	University of Cagliari	Italy	26

3.4. Journal and Co-cited Journals Analysis

Table 3 delineates the leading journals contributing to research on LID between 2015 and 2024, ranked by publication volume. Movement Disorders emerged as the foremost outlet with 54 articles (Impact Factor: 7.6), followed by Neurobiology of Disease (34 articles, IF: 5.6) and Neuropharmacology (32 articles, IF: 4.6). These three journals collectively represent the core academic platforms disseminating key findings

Rank	Country	Number of articles	Betweenness Centrality
4	CANADA	64	0.30
5	FRANCE	64	0.22
6	SPAIN	50	0.13
7	SWEDEN	45	0.11
8	BRAZIL	33	0.05
9	SOUTH KOREA	32	0.05
10	GERMANY	31	0.07

3.3. Institutional Analysis

For institutional analysis, we compiled all affiliations listed by authors to comprehensively capture the participation of research institutions. Through systematic manual verification, we standardized abbreviations, acronyms, and variant names into their corresponding official full names, thereby resolving inconsistencies in institutional naming. Table 2 presents the top five institutions ranked by the number of published papers on LID. In total, 269 institutions contributed to research in this field. With respect to publication volume, the top-performing institutions were the Centre National de la Recherche Scientifique (CNRS), Lund University, and the University of Bordeaux, producing 49, 33, and 29 publications respectively, thereby occupying the leading positions.

in the field during this period. Notably, Movement Disorders leads with 2,369 citations, confirming its central role in movement disorder research (Table 4). Following closely, the Journal of Neuroscience and Neurobiology of Disease received 1,062 and 876 citations respectively, indicating that fundamental analyses of neural mechanisms and their translational studies provide critical theoretical underpinnings for levodopa-induced dyskinesia. The top ten co-cited journals all possess an H-index ≥ 84 and a CiteScore ≥ 5.60 , representing high-quality publications that collectively form the authoritative

knowledge foundation of this field [5].

Table 3. Top 10 Journals with the most publications.

Rank	Journals	H-index	Impact Factor	Number of articles
1	Movement Disorders	174	7.6	54
2	Neurobiology Disease	151	5.6	34
3	Neuropharmacology	150	4.6	32
4	Journal of Neural Transmission	100	4.0	29
5	Experimental Neurology	168	4.2	21
6	Parkinsonism & Related Disorders	84	3.4	17
7	Journal of Parkinson's Disease	32	5.0	16
8	Neuroscience	204	2.8	15
9	Scientific Reports	149	3.9	13
10	Frontiers In Aging Neuroscience	55	4.5	12

Table 4. Top 10 Co-cited Journals with the most citations.

Rank	Journals	H-index	CiteScore	Citations
1	Movement Disorders	174	13.20	2369
2	Journal of Neuroscience	422	8.00	1062
3	Neurobiology of Disease	151	8.90	876
4	Neurology	331	10.20	780
5	Brain	308	20.4	632
6	Neuropharmacology	150	9.40	577
7	Experimental Neurology	168	8.70	534
8	Parkinsonism & Related Disorders	84	6.00	520
9	Annals of Neurology	273	15.90	516
10	Neuroscience	204	5.60	514

3.5. Authors and Co-cited Authors Analysis

A total of 2,864 co-cited authors contributed to the 691 research publications on LID in PD. Table 5 presents the top 10 most prolific authors along with their associated information. By examining publication output and collaboration networks, core authors and their academic influence within the field can be assessed from multiple perspectives (Figure 4). Huot P. was the most prolific author with 25 publications, followed by Bishop C. and Bezard E., who contributed 25 and 21 publications, respectively.

Table 5. The top 10 authors in Levodopa-Induced Dyskinesia.

Rank	Author	Number of articles	Total link strength
1	Huot P.	25	97
2	Bishop C.	25	28
3	Bezard E.	21	34
4	Hamadjida A.	17	81

Rank	Author	Number of articles	Total link strength
5	Fox S. H.	17	26
6	Frouni I.	16	74
7	Chung S. J.	16	51
7	Li Q.	16	29
9	Calabresi P.	15	29
10	Cenci M. A.	15	6

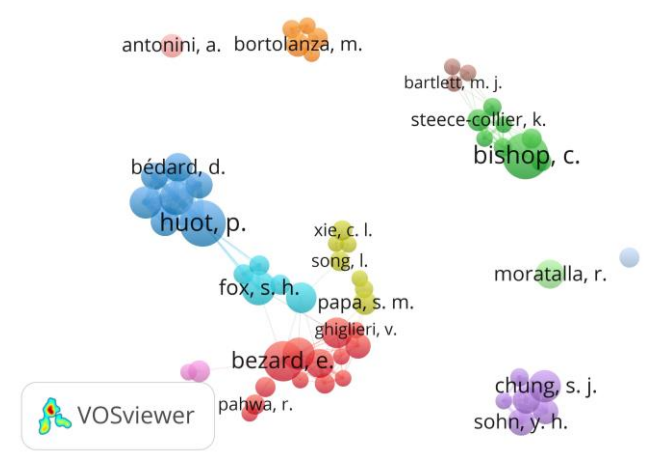


Figure 4. Co-author network in the field of Levodopa-Induced Dyskinesia. Analyzing publication data from 2015–2024 with VOSviewer yields a co-occurrence network where node size indicates an author’s publication volume, and link strength reflects the intensity of collaboration.

3.6. Hotspot and Frontier Analysis

3.6.1. Keyword Frequency and Cluster Analysis

Analysis of high-frequency keywords reveals the evolving research hotspots and emerging frontiers in this field (Figure 5), the most frequent keywords included “Levodopa induced dyskinesia” (676), “Parkinson’s disease” (621), and “Levodopa” (590) (Table 6). The high co-occurrence intensity of the thematic phrase “Levodopa-induced dyskinesia” with “Parkinson’s disease” indicates that academia consistently examines dyskinesia within the overall disease progression framework of Parkinson’s disease. As a core pathogenic factor and intervention target, “Levodopa” follows immediately in frequency after the thematic phrase, suggesting that the dual role of the drug itself has become a research consensus. Concurrently, “Drug therapy” ranks fourth, reflecting that pharmacological strategies to improve or prevent LID remain the mainstream direction. Meanwhile, “Disease models” occupies the fifth position, highlighting the critical supporting role of animal and cellular models in elucidating mechanisms and translational validation. The clustered distribution of these high-frequency

keywords delineates a five-pronged research framework encompassing “disease-drug-complication-intervention-model”, laying the groundwork for subsequent bibliometric analyses to delve into knowledge evolution pathways and emerging research frontiers.

Table 6. Co-occurrence Network of Research Keywords.

Rank	Keywords	Counts
1	Levodopa induced dyskinesia	676
2	Parkinson’s disease	621
3	Levodopa	590
4	Drug therapy	417
5	Disease models	392

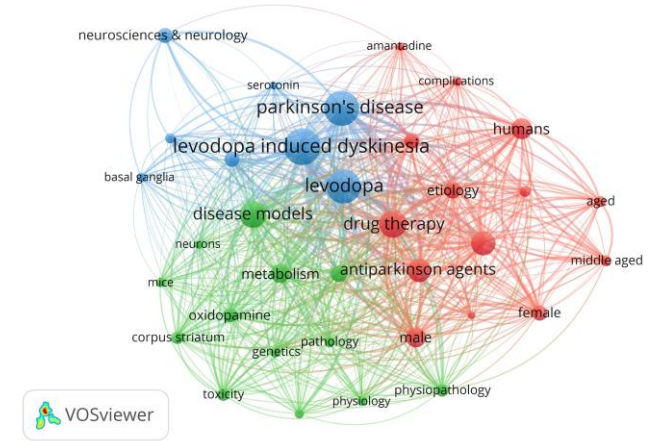


Figure 5. Keyword co-occurrence network in Levodopa-Induced Dyskinesia research. Generated with VOSviewer (2015–2024), the map visualizes thematic linkages based on keyword co-occurrence. Larger nodes indicate higher frequency keywords, highlighting central research themes.

Co-occurrence analysis conducted with CiteSpace generated a well-structured keyword clustering map (Modularity Q = 0.5135; Weighted Mean Silhouette S = 0.7803) (Figure 6), in which “levodopa-induced dyskinesia” emerged as a central and cross-cutting research theme. Typically, a Q-value exceeding 0.3 indicates a significantly modular network with clearly defined subdomains, while an S-value above 0.7 reflects high internal consistency within clusters, supporting the robustness and reliability of the results. Key clusters include #0 Neurosciences & Neurology, providing the broad disciplinary foundation [6-9]; #1 Disease Models, underpinning pre-clinical mechanistic and therapeutic exploration [10-20]; #2 Middle Aged, highlighting early-onset Parkinson’s as a key risk factor [21, 22]; #3 Parkinson Disease/Drug Therapy, focusing on treatment optimization [16, 23-31]; #4 Levodopa

Toxicity, investigating molecular and neuroadaptive mechanisms [32-34]; and #5 Substantia Nigra, examining the prerequisite role of dopaminergic degeneration [35-38]. Together, these clusters form an integrated framework spanning fundamental mechanisms to clinical management.

The current research landscape reflects three major translational shifts: first, a move from reactive symptom control toward proactive, mechanism-based prevention; second, an expansion from a primarily dopamine-centric view to multi-system targeting; and third, a transition from generalized treatment strategies

toward personalized medicine based on biomarkers and patient stratification. Nevertheless, several research gaps persist, including the underexplored role of the gut-brain axis, the influence of gender differences, the application of digital health technologies for monitoring, and the development of non-invasive neuro-modulation approaches. Future work should prioritize these areas through interdisciplinary collaboration to ultimately translate mechanistic understanding into improved clinical outcomes.

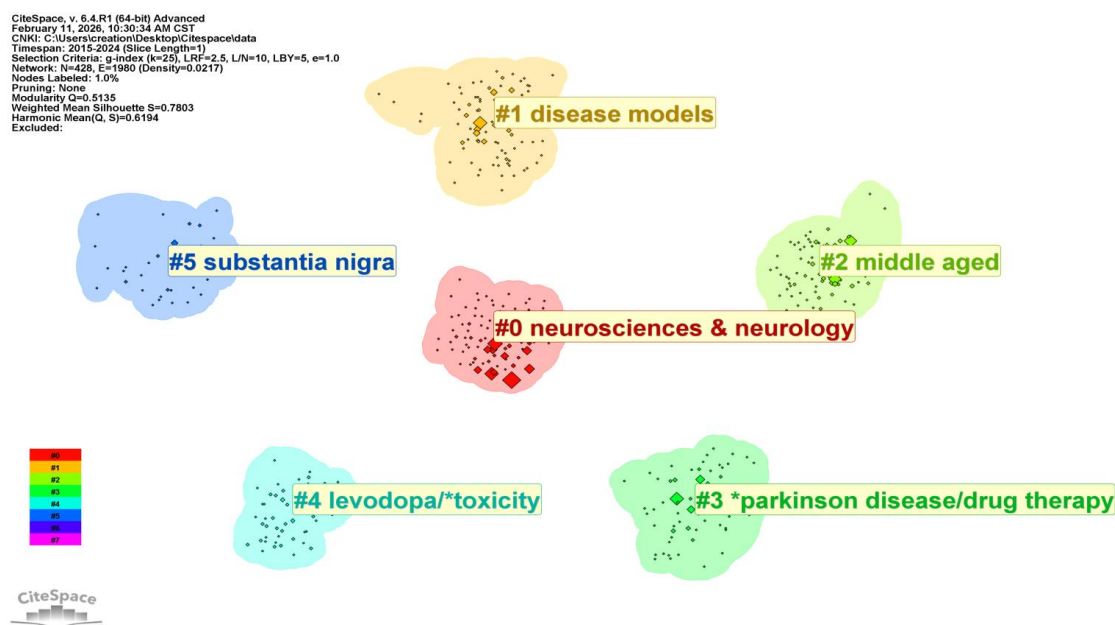


Figure 6. Keyword cluster analysis map of Levodopa-Induced Dyskinesia research. The cluster structure is validated as highly efficient and significant, with a silhouette coefficient (S) of 0.7803 and a modularity (Q) of 0.5135. Using the LLR algorithm on the keyword co-occurrence matrix, six distinct research subdomains were identified: disease models, middle-aged populations, neuroscience fundamentals, levodopa toxicity, Parkinson's disease pharmacotherapy, and substantia nigra lesions.

3.6.2. Keyword Emergence Analysis

Keyword emergence analysis conducted with CiteSpace reveals distinct thematic shifts in LID research from 2015 to 2024 (Figure 7). During the early stage (2015–2018), the most prominent keywords included “Parkinson disease/drug therapy” (Strength=3.88), “retrospective studies” (Strength=3.81), and “drug-induced/drug therapy/etiology” (Strength=5.19). Research in this phase centered on evidence-based summarization and etiological investigation, with extensive use of large-scale retrospective analyses to assess long-term levodopa efficacy and adverse reactions. The strong emergence of “drug-induced/drug therapy/etiology” further reflected scholarly attention to the causal role of pharmacotherapy in disease progression, particularly the temporal relationship between levodopa administration and the development of motor complications.

From 2019 to 2024, the keyword landscape shifted markedly, with leading emergent terms including “parkinson disease/drug therapy” (13.34), “levodopa/adverse effects” (12.22), and “antiparkinson agents/adverse effects” (5.74). This transition signifies an evolution from macro-epidemiological description toward refined safety evaluation and mechanistic investigation. The heightened intensity of “parkinson disease/drug therapy” indicates the growing dominance of systematic reviews and meta-analyses aimed at integrating multi-center evidence to optimize treatment regimens. Concurrently, the persistent emergence of terms related to adverse effects underscores sustained academic concern regarding dyskinesia and neuropsychiatric side effects induced by levodopa and other antiparkinson agents. Research in this phase increasingly employs genomics, neuroimaging, and other advanced methodologies to identify individual susceptibility factors, delineate dose-response relationships, and evaluate alternative therapeutic options.

In summary, contemporary LID research reflects a multi-disciplinary and multi-level investigative approach, spanning molecular mechanisms, neural circuitry, interventional therapies, and intelligent assessment technologies. This integrated

perspective provides a robust foundation for developing personalized treatment strategies and deepening the pathophysiological understanding of dyskinesia.

Top 15 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2015 - 2024
*parkinson disease/drug therapy	2020	13.34	2021	2024	
levodopa/adverse effects	2015	12.22	2022	2024	
drug-induced/drug therapy	2020	6.85	2022	2024	
antiparkinson agents/adverse effects	2015	5.74	2022	2024	
antiparkinson agents/therapeutic use	2017	5.52	2022	2024	
drug-induced/drug therapy/etiology	2021	5.19	2021	2024	
corpus striatum	2020	4.6	2020	2024	
parkinson disease/drug therapy	2015	3.88	2017	2018	
retrospective studies	2017	3.81	2017	2020	
levodopa/therapeutic use	2015	3.65	2022	2024	
biochemistry & molecular biology	2021	3.64	2021	2024	
corpus striatum/metabolism	2015	3.58	2021	2024	
drug-induced/*drug therapy/etiology	2016	3.48	2017	2019	
motor activity/drug effects	2015	3.3	2015	2016	
*parkinson disease/drug therapy/genetics	2021	3.19	2021	2024	

Figure 7. Temporal hotspots in LID research based on citation bursts. The 15 keywords with the highest burst strength between 2015 and 2024 were identified. For each keyword, the corresponding red bar represents the active period of its citation surge, mapping the dynamic landscape of research interest.

3.6.3. Peak Cluster Analysis of Keyword Clusters

Based on the keyword cluster peak map generated by CiteSpace (Figure 8), research themes in LID in PD exhibited a progressive evolution from “mechanism exploration → model validation → clinical intervention” between 2015 and 2024.

During 2015–2016, Cluster #0 (neurosciences & neurology) formed earliest and demonstrated the longest duration, peaking in 2015. This reflects the initial research focus on fundamental mechanisms such as neurotransmitter imbalances and basal ganglia circuit dysfunction. Concurrently, the emergence of Cluster #5 (substantia nigra) underscored the central role of dopaminergic neuron degeneration in the nigrostriatal pathway as a core target of levodopa toxicity.

From 2016 to 2018, Cluster #1 (disease models) rose rapidly, reaching its peak in 2017. This trend indicates a shift toward systematic development and use of rodent and non-human primate models to validate dose-response relationships and gene-environment interactions underlying dyskinesia.

Between 2018 and 2020, Cluster #3 (Parkinson’s disease/drug therapy) grew significantly, peaking in 2020. This shift marked a transition in research emphasis from toxicity mechanisms to clinical intervention, with systematic reviews and real-world studies becoming prominent.

After 2020, both Cluster #3 (Parkinson’s disease/drug therapy) and Cluster #4 (levodopa/toxicity) experienced a second surge during 2021–2022, indicating renewed research interest in long-term levodopa-induced dyskinesia and non-motor symptoms. This phase has been accompanied by in-depth investigations into precise dose titration and alternative treatment strategies.

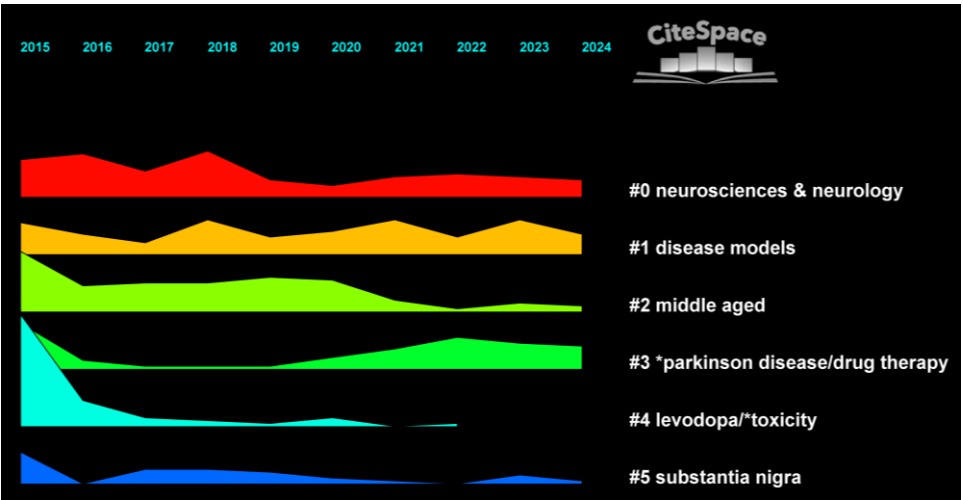


Figure 8. Landscape of keyword clusters over time. The CiteSpace timeline plot maps the dynamic evolution of six research clusters from 2015 to 2024. Larger nodes indicate higher annual publication output within a cluster, and the spanning color bands signify the period during which each thematic cluster was most active.

3.7. Co-cited References Analysis

Highly cited literature forms the core foundation in the field of LID. The review article “Pathophysiology of Levodopa-Induced Motor and Nonmotor Complications in Parkinson's Disease” (Bastide et al., 2015) published in *Advances in Neurobiology* ranks among the most frequently cited works (Table 7). It systematically elucidates the clinical characteristics, pathological mechanisms (e.g., dopamine receptor pulsatile

stimulation, neurotransmitter system abnormalities) and existing therapeutic approaches (e.g., amantadine, DBS). Similarly, highly cited is the *Nature Medicine* paper “Alleviating Levodopa-Induced Dyskinesia by Normalizing Dopamine D3 Receptor Function” (Bezard et al., 2003), which confirms the pivotal role of D3 receptor dysfunction and provides a rationale for targeted therapies. These publications establish the core framework for LID research, laying the groundwork for subsequent exploration of novel therapeutic targets.

Table 7. The top 5 Co-cited references in Levodopa-Induced Dyskinesia.

Rank	Title	Year	Journal	IF	CiteScore	Citation times
1	Pathophysiology of L-dopa-induced motor and non-motor complications in Parkinson's disease	2015	Progress in Neurobiology	6.1	13.90	74
2	Levodopa-induced dyskinesia in Parkinson disease: Current and evolving concepts	2018	Annals of Neurology	7.7	15.90	44
3	Eltoprazine counteracts l-DOPA-induced dyskinesias in Parkinson's disease: a dose-finding study	2015	Brain	11.7	20.40	30
4	Dopamine D3 Receptor Modulates L-DOPA-Induced Dyskinesia by Targeting D1 Receptor-Mediated Striatal Signaling	2017	Cerebral Cortex	2.9	5.80	27
5	Amantadine extended release for levodopa-induced dyskinesia in Parkinson's disease	2015	Movement Disorders	7.6	13.20	25

4. Discussion

This study examines research hotspots and developmental trends of LID in PD through a bibliometric analysis of 691 articles published between 2015 and 2024, sourced from the Web of Science Core Collection and PubMed.

4.1. General Trends and Global Contributions

Annual publication output from 2015 to 2024 displayed a pattern of initial trend of decline, followed by growth and a subsequent decrease, with each fluctuation reflecting evolving research priorities and resource allocation. Geographically, the United States led in both publication volume and betweenness centrality, indicating its central role in global research collaboration. Among the top ten most productive countries, nine were developed nations, with China being the only developing country. Although China entered the field later, it has shown rapid development. However, its relatively low betweenness centrality (0.21) suggests limited integration with established research networks dominated by developed countries, pointing to the need for enhanced international collaboration [39]. Among the top ten authors by output, Huot P. ranked highest in both publications and collaborative linkages, indicating a focused and influential research trajectory.

4.2. Hot Topic Analysis

Analysis of keyword frequency reveals a strong interdisciplinary connection between PD research and the broader fields of neuroscience and neurology, with "Parkinson's disease", "neurosciences & neurology", and "levodopa-induced dyskinesia" representing core research themes. The analysis further demonstrates that LID has evolved into a central focus in the study of Parkinson's disease complications, with research priorities undergoing a distinct thematic shift from basic mechanism exploration to clinical translation over the past decade.

The research evolution unfolded through two sequential phases. During the 2015–2018 mechanism exploration phase, investigation centered on neuromolecular mechanisms and animal model development, as evidenced by keywords related to dopamine metabolism, synaptic plasticity, and early gene expression. From 2019 to 2024, the focus transitioned to clinical translation and personalized therapy, marked by emerging emphasis on drug therapy optimization, toxicity management, and non-pharmacological interventions. This shift was driven by multiple factors including growing clinical demand, therapeutic innovations, updated clinical guidelines, safety concerns regarding long-term levodopa use, and the need for pharmacological optimization.

Recent advances in genetic research, particularly regarding COMT and DRD2 polymorphisms, have further facilitated the development of personalized treatment strategies. This translational trend is clearly reflected in contemporary clinical

guidelines such as the 2024 DGN Guidelines, which emphasize multimodal assessment, combined treatment approaches, and patient-centered care. The continuous evolution from basic research to precision medicine underscores a maturing research paradigm that effectively bridges laboratory findings with clinical applications to address the complex challenges of LID management.

4.3. Research Limitations

While this study provides valuable insights into research trends in LID through analysis of 691 articles from Web of Science Core Collection and PubMed databases, several limitations should be acknowledged.

First, the study did not perform citation analysis due to technical constraints in processing PubMed data with VOSviewer. Institutional analysis was conducted separately for each database because technical limitations prevented merging Web of Science and PubMed datasets in CiteSpace. Additionally, the preliminary literature retrieval process could not undergo thorough manual screening due to workflow constraints, potentially resulting in duplicate or erroneous institutional affiliation information. These factors collectively affected the accuracy and comprehensiveness of the institutional collaboration network analysis.

Moreover, the study's scope was limited to two databases; incorporating additional sources such as Scopus could broaden the investigative scope [40]. Furthermore, keyword and temporal trend analysis may not fully capture the underlying motivations for research or specific methodological details. Finally, while bibliometric analysis effectively identifies macro-level trends, its utility for meso- and micro-level analysis remains limited.

Therefore, future research would benefit from more rigorous data cleaning and integration methodologies to enhance reliability, as well as expansion to include additional databases and more nuanced analytical approaches.

5. Conclusion

This bibliometric analysis delineates the evolving research landscape of LID in PD from 2015 to 2024, revealing a clear transition from initial mechanistic and animal model studies toward clinical translation and personalized therapeutic strategies. The field exhibits three defining translational shifts: from symptomatic control to mechanism-based prevention, from dopamine-centric approaches to multi-system targeting, and from generalized treatment to biomarker-guided precision medicine. While developed countries currently dominate research output, significant opportunities exist for expanded international collaboration. Emerging research fronts—including the gut-brain axis, gender-specific susceptibility factors, digital monitoring technologies, and non-invasive neuromodulation—represent promising avenues for future investigation. These findings collectively provide a systematic framework

for guiding subsequent research toward addressing unresolved clinical challenges and advancing therapeutic paradigms for LID management. Future research on levodopa-induced dyskinesia may focus on exploring novel therapies targeting non-dopaminergic pathways (such as adenosine and glutamate receptors), developing precision dosing and personalized treatment strategies, and delving deeper into potential mechanisms involving gut microbiota and neuroimmunology.

Abbreviations

LID	Levodopa-Induced Dyskinesia
CNRS	Centre National de la Recherche Scientifique
PD	Parkinson's Disease
WoSCC	Web of Science Core Collection
DBS	Deep Brain Stimulation
Levodopa	L-3, 4-dihydroxyphenylalanine
USA	The United States
DOIs	Digital Object Identifiers

Author Contributions

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Funding

This research was mainly supported by grants from Funding by Science and Technology Projects in Guangzhou (grant number 2024A03J0818), and Guangdong Basic and Applied Basic Research Foundation (grant number 2024A1515013205).

Conflicts of Interest

The authors declare no competing interests.

References

- [1] Zhu J, C. Y. et al. Temporal trends in the prevalence of Parkinson's disease from 1980 to 2023: a systematic review and meta-analysis. *The Lancet Healthy Longevity*. 2024, 5, e464-e479. [https://doi.org/10.1016/s2666-7568\(24\)00094-1](https://doi.org/10.1016/s2666-7568(24)00094-1)
- [2] Sharma, S. et al. Neurobiology of L-DOPA induced dyskinesia and the novel therapeutic strategies. *Biomedicine & Pharmacotherapy*. 2015, 70, 283-293. <https://doi.org/10.1016/j.biopha.2015.01.029>
- [3] Van Eck, N. J., Waltman, L. Software survey: VOSviewer, a computer program for bibliometric mapping. *Scientometrics*. 2010, 84(2), 523-538. <https://doi.org/10.1007/s11192-009-0146-3>
- [4] Chen, C. CiteSpace II: Detecting and Visualizing Emerging Trends and Transient Patterns in Scientific Literature. *Journal of the American Society for Information Science and Technology*. 2006, 57(3), 359-377. <https://doi.org/10.1002/asi.20317>
- [5] Chen, Y.-J., et al. Microglia-associated research in Parkinson's disease: a bibliometric analysis. *Frontiers in Aging Neuroscience*. 2025, 17, 1657349. <https://doi.org/10.3389/fnagi.2025.1657349>
- [6] Phillips, J. R. et al. Neural substrates and potential treatments for levodopa-induced dyskinesias in Parkinson's disease. *Reviews in the Neurosciences*. 2016, 27(7), 729-738. <https://doi.org/10.1515/revneuro-2016-0009>
- [7] Ryu, H.-S., et al. Genomic Analysis Identifies New Loci Associated With Motor Complications in Parkinson's Disease. *Frontiers in Neurology*. 2020, 11, 570. <https://doi.org/10.3389/fneur.2020.00570>
- [8] Jung, J. H. et al. White matter connectivity networks predict levodopa-induced dyskinesia in Parkinson's disease. *Journal of Neurology*. 2022, 269(6), 2948-2960. <https://doi.org/10.1007/s00415-021-10883-1>
- [9] Wang, P.-F., et al. Fenobam modulates distinct electrophysiological mechanisms for regulating excessive gamma oscillations in the striatum of dyskinetic rats. *Experimental Neurology*. 2024, 378, 114833. <https://doi.org/10.1016/j.expneurol.2024.114833>
- [10] Johnston, T. M. and S. H. Fox, Symptomatic Models of Parkinson's Disease and L-DOPA-Induced Dyskinesia in Non-human Primates. *Curr Top Behav Neurosci*. 2015, 22, 221-35. https://doi.org/10.1007/7854_2014_352
- [11] Ba, M. M. Kong, and G. Ma, Postsynaptic density protein 95-regulated NR2B tyrosine phosphorylation and interactions of Fyn with NR2B in levodopa-induced dyskinesia rat models. *Drug Des Devel Ther*. 2015, 9, 199-206. <https://doi.org/10.2147/dddt.S75495>
- [12] Bortolanza, M. et al. Glial activation is associated with l-DOPA induced dyskinesia and blocked by a nitric oxide synthase inhibitor in a rat model of Parkinson's disease. *Neurobiol Dis*. 2015, 73, 377-87. <https://doi.org/10.1016/j.nbd.2014.10.017>
- [13] Dekundy, A. et al. Effects of dopamine uptake inhibitor MRZ-9547 in animal models of Parkinson's disease. *J Neural Transm (Vienna)*. 2015, 122(6), 809-18. <https://doi.org/10.1007/s00702-014-1326-8>
- [14] Divito, C. B. et al. Loss of VGLUT3 Produces Circadian-Dependent Hyperdopaminergia and Ameliorates Motor Dysfunction and l-Dopa-Mediated Dyskinesias in a Model of Parkinson's Disease. *J Neurosci*. 2015, 35(45), 14983-99. <https://doi.org/10.1523/jneurosci.2124-15.2015>

- [15] Fidalgo, C. et al. Effect of serotonin transporter blockade on L-DOPA-induced dyskinesia in animal models of Parkinson's disease. *Neuroscience*. 2015, 298, 389-96. <https://doi.org/10.1016/j.neuroscience.2015.04.027>
- [16] Iderberg, H. et al. Activity of serotonin 5-HT (1A) receptor 'biased agonists' in rat models of Parkinson's disease and L-DOPA-induced dyskinesia. *Neuropharmacology*. 2015, 93, 52-67. <https://doi.org/10.1016/j.neuropharm.2015.01.012>
- [17] Mellone, M. et al. NMDA receptor GluN2A/GluN2B subunit ratio as synaptic trait of levodopa-induced dyskinesias: from experimental models to patients. *Frontiers In Cellular Neuroscience*. 2015, 9. <https://doi.org/10.3389/fncel.2015.00245>
- [18] Potts, L. F. et al. Dual κ -agonist/ μ -antagonist opioid receptor modulation reduces levodopa-induced dyskinesia and corrects dysregulated striatal changes in the nonhuman primate model of Parkinson disease. *Ann Neurol*. 2015, 77(6), 930-41. <https://doi.org/10.1002/ana.24375>
- [19] Shen, W. et al. M4 Muscarinic Receptor Signaling Ameliorates Striatal Plasticity Deficits in Models of L-DOPA-Induced Dyskinesia. *Neuron*. 2015, 88(4), 762-73. <https://doi.org/10.1016/j.neuron.2015.10.039>
- [20] Urs, N. M. et al. Targeting β -arrestin2 in the treatment of L-DOPA-induced dyskinesia in Parkinson's disease. *Proc Natl Acad Sci U S A*. 2015, 112(19), E2517-26. <https://doi.org/10.1073/pnas.1502740112>
- [21] Haaxma, C. A. et al. Risk of Disabling Response Fluctuations and Dyskinesias for Dopamine Agonists Versus Levodopa in Parkinson's Disease. *Journal Of Parkinsons Disease*. 2015, 5(4), 847-853. <https://doi.org/10.3233/JPD-150532>
- [22] Lenderking, W. R. et al. Assessment of Parkinson's disease levodopa-induced dyskinesia: a qualitative research study. *Qual Life Res*. 2015, 24(8), 1899-910. <https://doi.org/10.1007/s11136-015-0925-7>
- [23] Alam, M. R. and S. Singh, Neuromodulation in Parkinson's disease targeting opioid and cannabinoid receptors, understanding the role of NLRP3 pathway: a novel therapeutic approach. *Inflammopharmacology*. 2023, 31(4), 1605-1627. <https://doi.org/10.1007/s10787-023-01259-0>
- [24] Oertel, W. et al. Randomized, placebo-controlled trial of ADS-5102 (amantadine) extended-release capsules for levodopa-induced dyskinesia in Parkinson's disease (EASE LID 3). *Mov Disord*. 2017, 32(12), 1701-1709. <https://doi.org/10.1002/mds.27131>
- [25] Pahwa, R. et al. ADS-5102 (Amantadine) Extended-Release Capsules for Levodopa-Induced Dyskinesia in Parkinson Disease (EASE LID Study): A Randomized Clinical Trial. *Jama Neurol*. 2017, 74(8), 941-949. <https://doi.org/10.1001/jamaneurol.2017.0943>
- [26] Choi, H. and S. H. Koh, Understanding the role of glycogen synthase kinase-3 in L-DOPA-induced dyskinesia in Parkinson's disease. *Expert Opin Drug Metab Toxicol*. 2018, 14(1), 83-90. <https://doi.org/10.1080/17425255.2018.1417387>
- [27] Lopez-Lopez, A. et al. Rho kinase inhibitor fasudil reduces L-DOPA-induced dyskinesia in a rat model of Parkinson's disease. *Br J Pharmacol*. 2020, 177(24), 5622-5641. <https://doi.org/10.1111/bph.15275>
- [28] Bariotto-Dos-Santos, K., et al. Rating L-DOPA-Induced Dyskinesias in the Unilaterally 6-OHDA-Lesioned Rat Model of Parkinson's Disease. *Journal of Visualized Experiments*. 2021, (176), 62924. <https://doi.org/10.3791/62924>
- [29] Negida, A. et al. Mavoglurant (AFQ056) for the treatment of levodopa-induced dyskinesia in patients with Parkinson's disease: a meta-analysis. *Neurol Sci*. 2021, 42(8), 3135-3143. <https://doi.org/10.1007/s10072-021-05319-7>
- [30] Hansen, C. A. et al. Levodopa-induced dyskinesia: a historical review of Parkinson's disease, dopamine, and modern advancements in research and treatment. *J Neurol*. 2022, 269(6), 2892-2909. <https://doi.org/10.1007/s00415-022-10963-w>
- [31] Kwon, D. K., et al. Levodopa-Induced Dyskinesia in Parkinson's Disease: Pathogenesis and Emerging Treatment Strategies. *Cells*. 2022, 11(23), 3736. <https://doi.org/10.3390/cells11233736>
- [32] Wang, Q. and W. Zhang, Maladaptive Synaptic Plasticity in L-DOPA-Induced Dyskinesia. *Front Neural Circuits*. 2016, 10, 105. <https://doi.org/10.3389/fncir.2016.00105>
- [33] Cerovic, M. et al. Derangement of Ras-guanine nucleotide-releasing factor 1 (Ras-GRF1) and extracellular signal-regulated kinase (ERK) dependent striatal plasticity in L-DOPA-induced dyskinesia. *Biol Psychiatry*. 2015, 77(2), 106-15. <https://doi.org/10.1016/j.biopsych.2014.04.002>
- [34] Dyavar, S. R. et al. Transcriptomic approach predicts a major role for transforming growth factor beta type 1 pathway in L-Dopa-induced dyskinesia in parkinsonian rats. *Genes Brain Behav*. 2020, 19(8), e12690. <https://doi.org/10.1111/gbb.12690>
- [35] Brugnoli, A. et al. Genetic deletion of Rhes or pharmacological blockade of mTORC1 prevent striato-nigral neurons activation in levodopa-induced dyskinesia. *Neurobiol Dis*. 2016, 85, 155-163. <https://doi.org/10.1016/j.nbd.2015.10.020>
- [36] Caulfield, M. E. et al. Downregulation of striatal Ca (V)1.3 inhibits the escalation of levodopa-induced dyskinesia in male and female parkinsonian rats of advanced age. *Neurobiol Dis*. 2023, 181, 106111. <https://doi.org/10.1016/j.nbd.2023.106111>
- [37] Wang, Q. et al. Eltopazine prevents levodopa-induced dyskinesias by reducing causal interactions for theta oscillations in the dorsolateral striatum and substantia nigra pars reticulata. *Neuropharmacology*. 2019, 148, 1-10. <https://doi.org/10.1016/j.neuropharm.2018.12.027>
- [38] Brugnoli, A. C. A. Pisanò, and M. Morari, Striatal and nigral muscarinic type 1 and type 4 receptors modulate levodopa-induced dyskinesia and striato-nigral pathway activation in 6-hydroxydopamine hemilesioned rats. *Neurobiol Dis*. 2020, 144, 105044. <https://doi.org/10.1016/j.nbd.2020.105044>
- [39] Wei, Y., Tu, L., et al. Research hotspots and trends of transcranial magnetic stimulation in Parkinson's disease: a bibliometric analysis. *Frontiers in Neuroscience*. 2023, 17, 1280180. <https://doi.org/10.3389/fnins.2023.1280180>

- [40] Peng, J., Hao, C., Wan, H. Bibliometric analysis of rehabilitation in Alzheimer's disease (2000–2023): trends, hotspots and prospects. *Frontiers in Aging Neuroscience*. 2024, 16, 1457982. <https://doi.org/10.3389/fnagi.2024.1457982>