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THE NEUROPROTECTIVE EFFECTS OF L-DOPA VS DOPAMINE AGONISTS ON THE PROGRESSION PATTERN OF PARKINSON'S DISEASE : A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS AND PRIMARY STUDIES

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ABSTRACT

Background: Whether the initial choice between levodopa (L-Dopa) and a dopamine agonist (DA) modifies the biological course of Parkinson's disease (PD), rather than merely its symptomatic expression, remains one of the most persistent controversies in movement-disorder therapeutics. The historical hypotheses of L-Dopa-related oxidative toxicity and DA-mediated neuroprotection have never been reconciled with long-term clinical outcomes.

Objective: To synthesise randomised and non-randomised comparative evidence published within the last 15 years on the effects of L-Dopa versus DAs on neuroimaging and clinical markers of progression, motor complications, long-term disease milestones, patient-reported quality of life (QoL) and safety.

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Methods: This review followed PRISMA 2020. PubMed/MEDLINE, Europe PMC, Semantic Scholar and ClinicalTrials.gov were searched from 1 January 2011 to 13 November 2026. Randomised controlled trials (RCTs), comparative studies, cohorts and case series directly comparing L-Dopa-based with DA-based strategies were eligible. Risk of bias was assessed with RoB 2 and ROBINS-I. Random-effects (DerSimonian–Laird) models with Hartung–Knapp–Sidik–Jonkman (HKSJ) sensitivity analyses pooled hazard ratios (HR), risk ratios (RR), mean differences (MD) and Hedges g; certainty was rated with GRADE.

Results: Of 2,009 records, 11 studies (6 RCTs, 5 cohorts; 8,423 participants in relevant comparison arms) were included and 9 contributed to 10 quantitative syntheses. DA-first therapy reduced the hazard of dyskinesia/motor complications (HR 0.45, 95% CI 0.28–0.73; I^2 = 0%; low certainty), although the HKSJ interval crossed unity (0.16–1.28). No disease-modifying signal emerged: neuroimaging progression markers (g −0.16, −1.00 to 0.68), UPDRS-III change (MD −1.02, −3.77 to 1.74) and Hoehn–Yahr change did not differ. In the largest pragmatic RCT, levodopa-sparing therapy did not lower dementia (HR 1.23, 0.93–1.64), institutionalisation (HR 1.16, 0.85–1.59) or death (HR 1.18, 0.95–1.46). QoL was slightly worse with DAs (g 0.14, 0.04–0.24), discontinuation or failure of allocated therapy was more frequent (RR 3.15, 0.88–11.33; 2.14, 1.22–3.77 after excluding the dominant trial) and impulse control and related disorders were four-fold more frequent (ratio 4.15, 2.55–6.75).

Conclusion: Contemporary evidence does not support a neuroprotective advantage of DAs over L-Dopa, nor a neurotoxic effect of L-Dopa, on the progression pattern of PD. The benefit of

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DA-first therapy is confined to delayed dyskinesia and is offset by poorer tolerability, neuropsychiatric harm and marginally lower QoL. Initial therapy should be individualised on symptomatic, not disease-modifying, grounds.

Keywords: *Parkinson's disease; levodopa; dopamine agonists; neuroprotection; disease progression; dyskinesia; meta-analysis*

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INTRODUCTION

Parkinson's disease (PD) is the fastest-growing neurological disorder worldwide, with the number of affected individuals more than doubling between 1990 and 2016 and a disability burden that is projected to rise further as populations age. The disease is defined clinically by bradykinesia with rest tremor and/or rigidity, but its pathology extends far beyond the nigrostriatal pathway, encompassing α-synuclein aggregation in autonomic, limbic and cortical networks that underlie the non-motor and cognitive manifestations dominating its late stages.[1–4]

The selective vulnerability of substantia nigra pars compacta neurons has been attributed to their long, highly branched unmyelinated axons, autonomous pacemaking with cytosolic calcium loading and the oxidative chemistry of cytosolic dopamine. These features provided the biological rationale for two competing hypotheses that shaped the treatment of early PD for decades: that exogenous L-Dopa, by increasing dopamine turnover and the generation of reactive quinones, might accelerate degeneration, and that dopamine agonists (DAs), by reducing the requirement for dopamine synthesis and through putative mitochondrial and anti-apoptotic actions, might slow it.[5–7]

Levodopa remains the most efficacious symptomatic therapy, whereas non-ergot DAs (pramipexole, ropinirole, rotigotine) and, in some regions, ergot derivatives such as cabergoline are used as levodopa-sparing initial therapy, predominantly in younger patients. The rationale for levodopa sparing has rested on two separate arguments, namely delay of levodopa-induced dyskinesia and motor fluctuations, and the hypothetical modification of disease course. The first argument concerns a pharmacodynamic complication that reflects pulsatile stimulation of denervated striatal receptors and presynaptic loss of buffering capacity; the second concerns the biological rate of neurodegeneration itself, and the two are frequently conflated in clinical practice.[8–11]

Within the last 15 years, several pivotal studies have reframed this debate. Delayed-start trials of levodopa (LEAP) and of pramipexole (PROUD) found no evidence that either agent modifies disease progression, while observational data from sub-Saharan Africa indicated that motor complications are related to disease duration and levodopa dose rather than to the duration of levodopa exposure. Large longitudinal cohorts such as the Parkinson's Progression Markers Initiative (PPMI) have characterised the trajectories of clinical scales and dopamine transporter (DAT) imaging in early PD, demonstrating that imaging surrogates are themselves susceptible to pharmacological regulation.[12–15]

Contemporary guidelines from the American Academy of Neurology and the International Parkinson and Movement Disorder Society now recommend that the choice of initial therapy be individualised according to symptom burden, age, dyskinesia risk and susceptibility to DA-related adverse effects, rather than to any presumed disease-modifying property. Nonetheless, the question of whether L-Dopa and DAs exert divergent effects on the pattern of disease progression has not been addressed in an updated quantitative synthesis restricted to recent evidence and integrating randomised with real-world comparative data.[16–18]

Accordingly, this systematic review and meta-analysis aimed to compare L-Dopa-based and DA-based strategies with respect to (i) neuroimaging and clinical markers of disease progression, (ii) the incidence and timing of motor complications, (iii) long-term progression milestones including dementia, institutionalisation, need for device-aided therapy and mortality, (iv) patient-reported quality of life and (v) tolerability and neuropsychiatric safety, using randomised controlled trials (RCTs), comparative studies, cohorts and case series published from 2011 onwards.

METHODS

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and the methodological standards of the Cochrane Handbook for Systematic Reviews of Interventions. The protocol, including eligibility criteria, outcomes and analytic strategy, was defined a priori by the authors; it was not prospectively registered in a public registry, and this is acknowledged as a limitation.[19,20]

Eligibility was defined according to the PICOS framework summarised in Table 2. Studies were eligible if they enrolled patients with idiopathic PD and directly compared an L-Dopa-based strategy (L-Dopa monotherapy, L-Dopa-first therapy or L-Dopa optimisation) with a DA-based strategy (DA monotherapy, DA-first or levodopa-sparing therapy with DAs, or DA add-on), and reported at least one outcome related to disease progression, motor complications, long-term milestones, quality of life or safety. Only RCTs, non-randomised comparative studies, prospective or retrospective cohorts and case series published from January 2011 onwards were included, in keeping with the objective of prioritising contemporary evidence. Systematic reviews and meta-analyses were not included in the characteristics table or the quantitative synthesis but were retained for appraisal in the Discussion. Pre-clinical studies, cross-sectional analyses without a longitudinal outcome, single-arm extensions and studies in which the comparator was not L-Dopa were excluded.

The electronic search was performed on 13 November 2026 in four sources that returned retrievable and reproducible results: PubMed/MEDLINE, Europe PMC, Semantic Scholar and ClinicalTrials.gov. The search combined controlled vocabulary (Medical Subject Headings) and free-text terms for Parkinson's disease, L-Dopa, individual DAs and progression-related outcomes, with a publication window from 1 January 2011 to 13 November 2026 and no language restriction at the search stage. The full database-specific strategies, limits and yields are reported in Table 1. Reference lists of included studies and of relevant systematic reviews were hand-searched for additional reports, and trial registry entries were linked to their corresponding publications.

Table 1. Database-specific search strategies, limits and number of records retrieved (search date: 13 November 2026)

Database	**Search string**	**Limits / filters**	**Records**
PubMed/MEDLINE	("Parkinson Disease"[MeSH Terms] OR parkinson*[tiab]) AND ("Levodopa"[MeSH Terms] OR levodopa[tiab] OR "L-dopa"[tiab]) AND ("Dopamine Agonists"[MeSH Terms] OR "dopamine agonist*"[tiab] OR pramipexole[tiab] OR ropinirole[tiab] OR rotigotine[tiab] OR piribedil[tiab] OR bromocriptine[tiab] OR cabergoline[tiab]) AND (progression[tiab] OR neuroprotect*[tiab] OR "disease-modifying"[tiab] OR "disease modification"[tiab] OR "initial therapy"[tiab] OR "initial treatment"[tiab] OR "de novo"[tiab] OR "early Parkinson*"[tiab] OR "long-term"[tiab] OR dyskinesia*[tiab] OR "motor complication*"[tiab] OR "motor fluctuation*"[tiab] OR mortality[tiab] OR dementia[tiab] OR "dopamine transporter"[tiab]) AND ("2011/01/01"[dp] : "2026/11/13"[dp])	Publication date 2011/01/01–2026/11/13; all article types	685
Europe PMC	(TITLE:parkinson *OR*	Title/abstract fields;	534

	ABSTRACT:parkinson) AND (TITLE/ABSTRACT: levodopa OR "L-dopa") AND (TITLE/ABSTRACT: "dopamine agonist" OR "dopamine agonists" OR pramipexole OR ropinirole OR rotigotine OR piribedil OR bromocriptine OR cabergoline) AND (TITLE/ABSTRACT: progression OR neuroprotection OR neuroprotective OR "disease-modifying" OR "initial therapy" OR "initial treatment" OR "de novo" OR "long-term" OR dyskinesia OR dyskinesias OR "motor complications" OR "motor fluctuations" OR mortality OR dementia OR "dopamine transporter") AND (PUB_YEAR:[2011 TO 2026])	publication year 2011–2026; all sources (MED, PMC, PPR)	
Semantic Scholar	(levodopa | "L-dopa") + ("dopamine agonist" | pramipexole | ropinirole | rotigotine | cabergoline | piribedil | bromocriptine) + parkinson + (progression | neuroprotection | neuroprotective | "disease-modifying" | "initial therapy" | "de novo" | dyskinesia | "motor complications" | mortality | dementia | "dopamine transporter")	Bulk search; year 2011–2026	761
ClinicalTrials.gov	Condition: "Parkinson Disease"; Intervention: levodopa AND (pramipexole OR ropinirole OR rotigotine OR cabergoline OR piribedil OR bromocriptine OR "dopamine agonist")	Study start date 2011-01-01 to 2026-11-13; all statuses; with or without results	29
Total			2,009

Search engines that could not be queried reproducibly at the time of the search were not used and are therefore not reported. tiab, title/abstract field tag; dp, date of publication.

After automated and manual de-duplication based on PubMed identifiers, digital object identifiers and normalised titles, records were screened at the title and abstract level against the eligibility criteria, followed by assessment of full reports, registry records and supplementary material where available. Screening and eligibility assessment were performed independently by two reviewers, with disagreements resolved by discussion with the third author, who is a consultant neurologist.

Table 2. Eligibility criteria according to the PICOS framework

Domain	**Inclusion criteria**	**Exclusion criteria**
Population	Adults with idiopathic PD (any stage), including de novo, early, fluctuating and post-deep brain stimulation (DBS) populations	Atypical or secondary parkinsonism; restless legs syndrome; animal or in vitro models
Intervention	DA-based strategy: DA monotherapy, DA-first/levodopa-sparing initial therapy, DA add-on (pramipexole, ropinirole, rotigotine, piribedil, cabergoline, bromocriptine)	Apomorphine infusion or other device-aided therapy as the sole comparison; MAO-B inhibitor-only arms
Comparator	L-Dopa-based strategy: L-Dopa monotherapy, L-Dopa-first therapy or L-Dopa optimisation (including L-Dopa/COMT inhibitor)	Placebo-only comparator; comparator not containing L-Dopa (e.g., DA vs MAO-B inhibitor, DA vs amantadine)
Outcomes	Progression markers (DAT/18F-DOPA/FDG PET imaging, UPDRS/MDS-UPDRS change, Hoehn–Yahr); motor complications; long-term milestones (dementia, institutionalisation, DBS, mortality); QoL (PDQ-39); adverse events, discontinuation, neuropsychiatric events	Purely pharmacokinetic or mechanistic endpoints without clinical or imaging progression relevance
Study design	RCTs, non-randomised comparative studies, prospective/retrospective cohorts, case series	Systematic reviews and meta-analyses (discussed only), narrative reviews, editorials, case reports, cross-sectional studies, economic models
Time frame	Published 1 January 2011 to 13 November	Published before 2011

	2026	

COMT, catechol-O-methyltransferase; DA, dopamine agonist; DAT, dopamine transporter; MAO-B, monoamine oxidase type B; PDQ-39, 39-item Parkinson's Disease Questionnaire; QoL, quality of life; UPDRS, Unified Parkinson's Disease Rating Scale.

Data were extracted into a piloted form capturing first author, year, country, design, setting, population characteristics, sample size per arm, DA agent and dose, L-Dopa regimen, follow-up duration, outcome definitions and effect estimates with their measures of precision. Adjusted estimates were preferred over crude estimates for non-randomised studies. When full texts were not openly accessible, data were extracted from the published abstract, the trial registry results database or supplementary material, and this source is identified in the characteristics table. Registry-only results were included when posted results were complete and the trial was otherwise unpublished, in order to mitigate publication bias.

Risk of bias in RCTs was assessed with the revised Cochrane risk-of-bias tool (RoB 2) across five domains: the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. Non-randomised studies were appraised with ROBINS-I across seven domains (confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of the reported result), and their methodological quality was additionally summarised with the Newcastle–Ottawa Scale (NOS).[21,22]

Time-to-event outcomes were synthesised as hazard ratios (HR), dichotomous outcomes as risk ratios (RR) and continuous outcomes as mean differences (MD) when a common scale was used, or as standardised mean differences expressed as Hedges g when scales differed. All estimates were oriented so that values below 1 (ratios) or below 0 (differences) favour the DA-based strategy for adverse outcomes. Where a study reported the L-Dopa versus levodopa-sparing contrast, the HR and its confidence limits were inverted. When only baseline and follow-up standard deviations were available, the standard deviation of the change score was imputed assuming a correlation of 0.5, and when only a mean difference with a 95% confidence interval was reported, the standard error was derived from the interval, as recommended by the Cochrane Handbook. A continuity correction of 0.5 was applied to zero-event cells.[20]

Pooling used inverse-variance random-effects models with the DerSimonian–Laird estimator of between-study variance (τ^2). Because of the small number of studies per outcome, the Hartung–Knapp–Sidik–Jonkman (HKSJ) adjustment was applied as a sensitivity analysis, and 95% prediction intervals were calculated when at least three studies were available. Statistical heterogeneity was quantified with Cochran's Q and the I^2 statistic, interpreted as low (<25%),

moderate (25–75%) or substantial (>75%). Pre-specified sensitivity analyses comprised leave-one-out analysis, restriction to cohort or randomised designs, exclusion of the dominant trial and cumulative meta-analysis by publication year; a subgroup analysis compared early PD with fluctuating PD. In an exploratory synthesis, adjusted HRs and RRs for impulse control disorders were combined on the logarithmic scale as approximations of relative risk.[23]

Small-study effects and publication bias were explored visually with contour-enhanced funnel plots and statistically with Egger's regression test; because fewer than ten studies were available for every outcome, these tests were interpreted as descriptive only. The certainty of evidence for each outcome was rated according to the GRADE approach, beginning at high for RCTs and, when ROBINS-I was used, also at high with subsequent downgrading for risk of bias, so that non-randomised evidence was rated appropriately, and further downgraded for inconsistency, indirectness, imprecision and publication bias. All analyses were performed in Python 3 using NumPy, SciPy and Matplotlib with purpose-written, double-checked meta-analytic routines; two-sided p values below 0.05 were considered statistically significant.[24,25]

RESULTS

The database search identified 2,009 records (PubMed/MEDLINE 685, Europe PMC 534, Semantic Scholar 761 and ClinicalTrials.gov 29). After removal of 940 duplicates, 1,069 unique records were screened by title and abstract and 1,039 were excluded, most commonly because they were narrative or systematic reviews (n = 441), did not compare L-Dopa with a DA or addressed an irrelevant population, exposure or outcome (n = 464), were pre-clinical studies (n = 76), case reports (n = 34) or non-relevant registry entries (n = 24). Thirty reports were assessed in detail, of which 18 were excluded for the reasons listed in Table 3. Eleven studies reported in 12 records were included, comprising six RCTs and five cohort studies; nine studies contributed data to ten quantitative syntheses and two cohorts were synthesised narratively because their effect metrics could not be pooled (Figure 1). No eligible case series were identified. Six systematic reviews or meta-analyses identified during screening were set aside for appraisal in the Discussion.

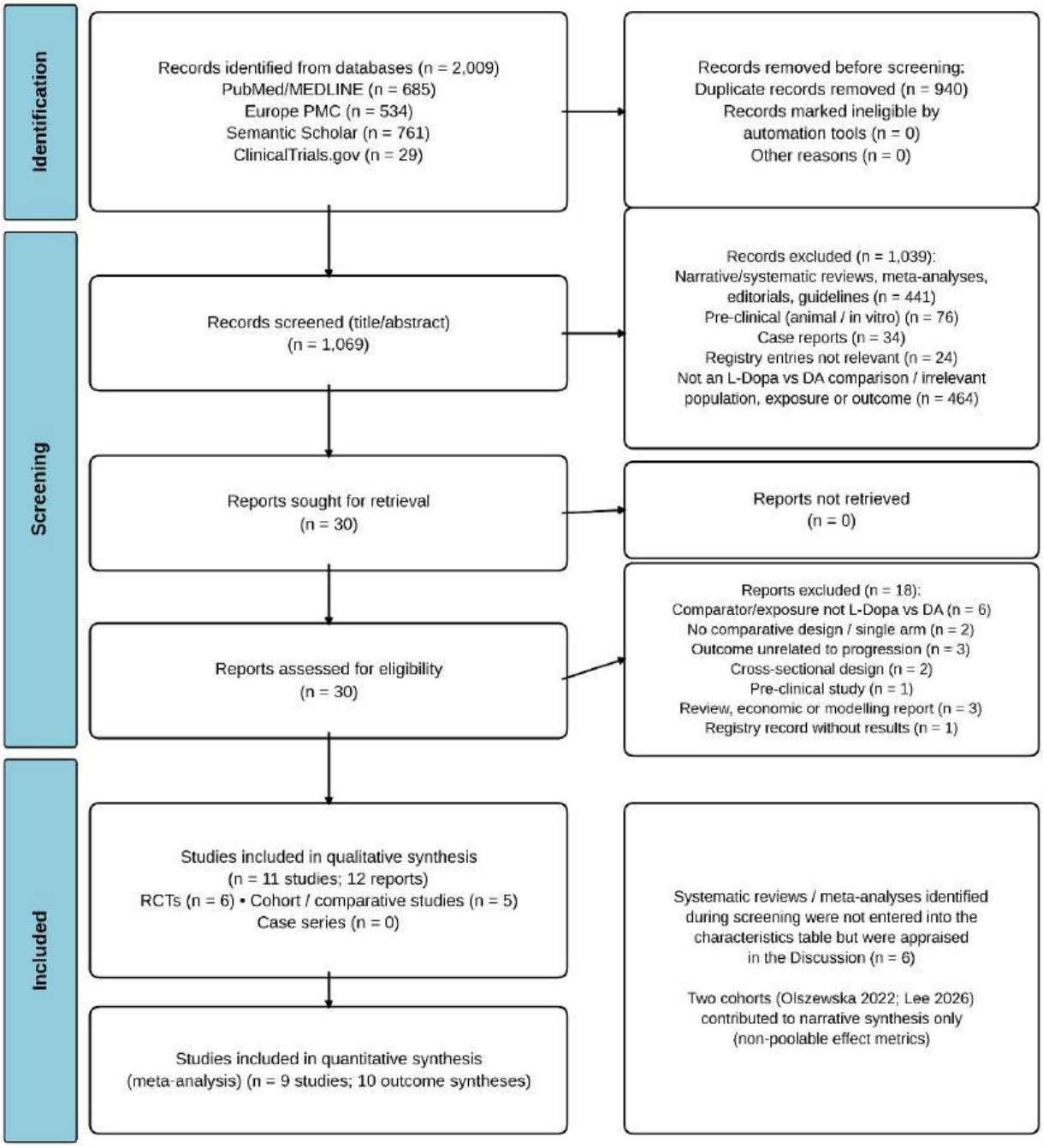


Figure 1. PRISMA 2020 flow diagram of study identification, screening, eligibility assessment and inclusion. Records were identified from four databases searched on 13 November 2026; the reasons for exclusion at each stage are shown in the right-hand boxes.

Table 3. Reports excluded after detailed eligibility assessment, with reasons

Report	**Design / focus**	**Principal reason for exclusion**
Depboylu et al., 2013	6-OHDA mouse model; long-term pramipexole vs L-Dopa with FP-CIT	Pre-clinical study

	SPECT	
Tvete & Klemp, 2022	Registry cohort; MAO-B inhibitor vs DA monotherapy and survival	Comparator not L-Dopa
Reese et al., 2015	Claims cohort; time-to-levodopa by initial drug class	Comparator not L-Dopa (outcome is L-Dopa initiation)
Gray et al., 2022 (PD MED adjuvant)	RCT; adjuvant DA vs COMT/MAO-B inhibitor in later PD	No L-Dopa-only comparator
Gungabissoon et al., 2020	Observational; prolonged- vs immediate-release DA	Comparator not L-Dopa
Schneider et al., 2019	Cohort; timing of dopaminergic treatment initiation	Exposure contrast is timing, not drug class
NCT01338662	Registry; amantadine vs DA and dyskinesia	Comparator not L-Dopa
Giladi et al., 2014	Open-label extension of rotigotine trials	Single-arm design; no comparator
NCT02227355	Registry; rotigotine + L-Dopa combination (observational)	No comparator arm; no results
Espay et al., 2019	PPMI analysis of mood effects of dopaminergic drugs	Outcome unrelated to progression or complications
Tveiten et al., 2013 (ParkWest)	Population cohort; 12-month symptomatic response	Symptomatic response only; arm-level data not extractable
Fanciulli et al., 2011	8-week lymphocyte DAT expression with DA vs L-Dopa	Peripheral surrogate without progression outcome
Politis et al., 2017	Cross-sectional [11C]raclopride PET	Cross-sectional design
Vieru et al., 2016	Cross-sectional serum uric acid by treatment group	Cross-sectional design
Piedad & Cavanna, 2012	Narrative review on pramipexole and dyskinesia	Review article
McIntosh et al., 2021	Cost-effectiveness analysis of PD	Economic evaluation

	MED	
Brehm et al., 2026	Decision-rule modelling of CALM-PD and STEADY-PD III data	Secondary modelling of pre-2011 trial data; no new comparative estimate
NCT01683253	Registry; switching DA to L-Dopa for ICD remission	Registry record without posted results

6-OHDA, 6-hydroxydopamine; COMT, catechol-O-methyltransferase; DA, dopamine agonist; DAT, dopamine transporter; ICD, impulse control disorder; MAO-B, monoamine oxidase type B; PPMI, Parkinson's Progression Markers Initiative.

The excluded reports comprised one pre-clinical study, six studies whose comparator or exposure contrast was not L-Dopa versus a DA, two non-comparative or single-arm reports, three studies whose outcomes were unrelated to progression or complications, two cross-sectional analyses, three review, economic or modelling reports and one registry entry without posted results (Table 3).[26–40]

The included studies were published between 2012 and 2026 and were conducted in Japan, Germany, the United Kingdom, the Netherlands, China, South Korea, Canada and France (Figure 2). The six RCTs comprised the large pragmatic PD MED trial, the 5-year CASTLE trial of cabergoline versus L-Dopa, an observer-blinded 18F-DOPA positron emission tomography (PET) trial, a pilot 18F-fluorodeoxyglucose (FDG) PET trial with registry-posted results, a rater-blinded trial of DA versus L-Dopa monotherapy after subthalamic deep brain stimulation (DBS) and a multicentre randomised comparison of DA add-on versus L-Dopa optimisation in patients with wearing-off. The five cohorts included a 15-year clinical inception cohort, a DAT-matched cohort, a DBS-referral cohort, the French NS-PARK multicentre cohort and a Korean nationwide claims cohort. Altogether, 8,423 participants contributed to the relevant comparison arms, with individual sample sizes ranging from 30 to 4,461 and follow-up from 8 weeks to approximately 15 years (Table 4 and Table 5).[41–51]

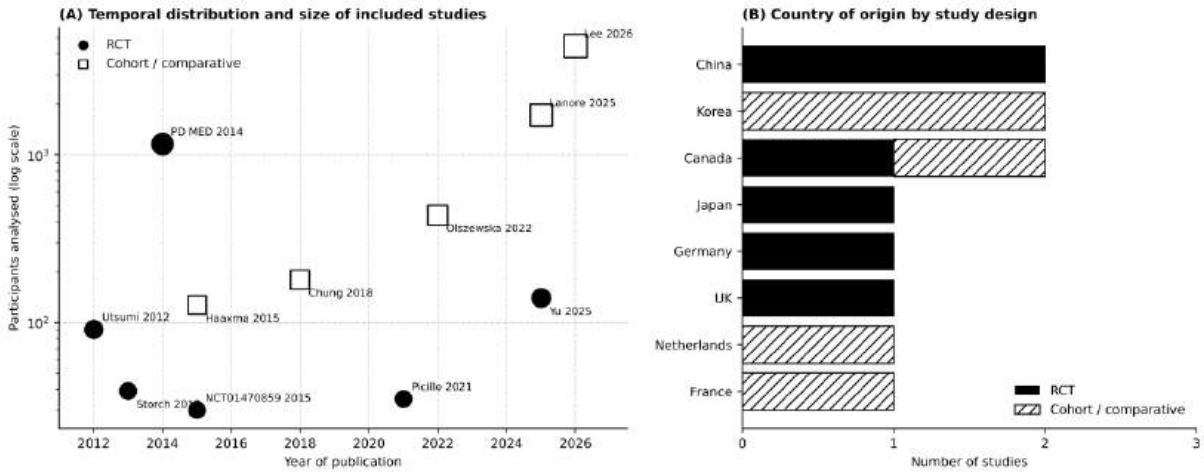


Figure 2. Distribution of the 11 included studies. (A) Year of publication against number of participants analysed (logarithmic scale); filled circles denote RCTs and open squares cohort or comparative studies. (B) Country of origin stratified by study design.

Table 4. Characteristics of the included studies

Study (ref.)	Country	Design	Population / setting	N (DA / L-Dopa)	DA strategy	L-Dopa strategy	Follow-up	Outcomes relevant to this review	Data source
Randomised controlled trials									
Utsumi 2012 (CASTLE)[4][1]	Japan	Open-label multicentre RCT	Drug-naïve early PD	91 (45 / 46)	Cabergoline monotherapy	L-Dopa monotherapy	5 years	Time to motor complications; adverse events	Abstract
Storch 2013[42]	Germany	Single-centre, observer-blinded parallel RCT	De novo PD	39 randomised; 35 analysed (17 / 18)	Cabergoline 3 mg/day	L-Dopa 300 mg/day	12 weeks	Putaminal 18F-DOPA PET effective distribution volume ratio (dopamine turnover); clinical scores	Abstract
PD MED 2014[43,52]	United Kingdom	Pragmatic open-label multicentre RCT	Newly diagnosed PD	1,620 randomised (632 DA, 460 MAO-BI, 528 L-Dopa)	Levodopa-sparing: clinician-selected DA (or MAO-BI)	L-Dopa	Median 3 y (≤7 y); 15-y update	PDQ-39 mobility, EQ-5D, dementia, institutionalisation, death, discontinuation,	Abstract; 15-y conference abstract

								dyskinesia	
NCT01470859 2015[44]	China	Open-label parallel pilot RCT	Early PD	30 (15 / 15); 29 analysed	Pramipexole 0.375–4.5 mg/day	L-Dopa/carbidopa CR 200–600 mg/day	12 months	18F-FDG PET PD-related pattern (PDRP), UPDRS-II/III, H&Y, PDQ-39, adverse events	Registry results
Picillo 2021[45]	Canada	Randomised, rater-blinded trial	PD 1 month after bilateral/unilateral STN-DBS	35 (18 / 17)	Pramipexole or ropinirole monotherapy	L-Dopa monotherapy	3 mo, 6 mo, ~2.5 y	NMSS, UPDRS-II/III/IV, PDQ-39, apathy, QUIP, monotherapy failure, ICD	Full text
Yu 2025[46]	China	Multicentre randomised (3:2) open-label study	PD with wearing-off on L-Dopa/benserazide	140 (56 / 84); 128 completed	L-Dopa/benserazide + pramipexole	Switch to L-Dopa/carbidopa/entacapone	8 weeks	Daily OFF/ON time, TEAEs, dyskinesia	Full text
Cohort and comparative studies									
Haaxma 2015[47]	Netherlands	Open prospective	Consecutive de novo PD,	127 (50 / 77)	DA-first	L-Dopa-first	Median 8.1 y	Onset of fluctuations,	Abstract

		clinical cohort	routine care				(1.1–17.7)	dyskinesia, disabling response fluctuations and dyskinesia (DRFD); motor scores	
Chung 2018[48]	South Korea	Retrospective matched cohort	Drug-naïve PD with baseline DAT PET	180 (90 / 90)	DA-first (L-Dopa added after 2.15 y)	L-Dopa-first	≥2 years	L-Dopa-induced dyskinesia (stratified Cox model)	Abstract
Olszewska 2022[49]	Canada	Retrospective cohort of DBS recipients	PD with disabling motor complications undergoing STN/GPi-DBS	438 (126 / 312)	DA-first	L-Dopa-first	Median ~10 y to surgery	Time from first treatment to DBS assessment and surgery	Abstract
Lanore 2025 (NS-PARK)[50]	France (26 centres)	Prospective multicentre cohort	PD <5 y duration without motor complications	1,722 (≈534 L-Dopa-alternative / ≈706 L-	L-Dopa-alternative therapy (DA and/or MAO-I)	L-Dopa monotherapy	Enrolment 2011–2021; interval-censore	Dyskinesia, fluctuations, ICRB, apathy, psychosis, daytime	Abstract

				Dopa monotherapy; 28% combinations)			d	sleepiness	
Lee 2026[51]	South Korea	Nationwide retrospective cohort (NHIS-Senior)	Newly diagnosed older adults with PD	4,461 (1,645 / 2,816)	Early adjunctive DA with L-Dopa	L-Dopa monotherapy	5 years	All-cause mortality (5-y restricted mean survival time)	Abstract

Group sizes for Lanore 2025 were derived from the reported proportions of the 1,722 participants. CR, controlled release; DA, dopamine agonist; DAT, dopamine transporter; DBS, deep brain stimulation; EQ-5D, EuroQol 5-dimension; GPi, globus pallidus internus; H&Y, Hoehn–Yahr stage; ICD, impulse control disorder; ICRB, impulse control and related behaviours; MAO-BI/MAO-I, monoamine oxidase (type B) inhibitor; NHIS, National Health Insurance Service; NMSS, Non-Motor Symptoms Scale; PDQ-39, 39-item Parkinson's Disease Questionnaire; QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; STN, subthalamic nucleus; TEAE, treatment-emergent adverse event.

Table 5. Outcome data extracted from the included studies (DA strategy versus L-Dopa strategy)

Study	**Outcome**	**DA strategy**	**L-Dopa strategy**	**Reported effect / statistic**	**Synthesis**
Utsumi 2012	Motor complications	4/45 (cumulative 17%)	11/46 (cumulative 34%)	HR 0.57 (0.18–1.81); p = 0.347	Figures 7–8
	Patients with adverse events	24/45 (35 events)	13/46 (16 events)	—	Figure 14
Storch 2013	Putaminal EDVR	−1.0 ± 13.0 (n = 17)	−8.3 ± 11.8 (n = 18)	Difference 7.3% (−1.2 to 15.8); p =	Figure 11

	change (%)			0.091	
PD MED 2014	Discontinuation for side effects	179/632 (28%)	11/528 (2%)	p < 0.0001	Figure 15
	PDQ-39 mobility	—	—	1.8 points (0.5–3.0) better with L-Dopa	Figure 13
	Dementia / institutionalisation / death	—	—	HR (L-Dopa vs sparing) 0.81 (0.61–1.08) / 0.86 (0.63–1.18) / 0.85 (0.69–1.06)	Figure 10
	15-year update	Dyskinesia 63%	Dyskinesia 70%	Dementia HR (L-Dopa vs sparing) 0.84 (0.73–0.98)	Figure 10 (sensitivity)
NCT01470859	PDRP Z-score change (12 mo)	0.61 ± 0.68 (n = 15)	0.41 ± 0.70 (n = 14)	p = 0.84	Figure 11
	UPDRS-III baseline → 12 mo	23.1 ± 10.4 → 24.3 ± 8.8	18.7 ± 7.7 → 19.5 ± 7.0	p = 0.874 at 12 mo	Figure 12
	UPDRS-II baseline → 12 mo	7.1 ± 2.9 → 8.4 ± 3.0	7.3 ± 3.5 → 7.4 ± 3.5	p = 0.635 at 12 mo	Figure 12
	H&Y baseline → 12 mo	1.43 ± 0.51 → 1.82 ± 0.54	1.35 ± 0.42 → 1.65 ± 0.47	p = 0.430 at 12 mo	Text
	PDQ-39 baseline → 12 mo	20.36 ± 16.49 → 21.07 ± 12.96	19.38 ± 10.94 → 20.36 ± 16.49	p = 0.867	Figure 13
	Adverse events / somnolence / non-completion	2/15 / 2/15 / 0/15	4/14 / 0/14 / 1/14	—	Figures 14–16
Picillo 2021	Monotherapy failure (3	11/18 / 15/18	3/17 / 6/17	p = 0.022 / p = 0.010	Figure 15

	mo / 6 mo)				
	Monotherapy maintained at ~2.5 y	0/18	8/17	Median time to failure 7.4 vs 47.8 mo; p = 0.005	Text
	New-onset ICD	4/18 (22.2%)	0/17	—	Figure 16
	UPDRS-III / UPDRS-II / UPDRS-IV / PDQ-39 (3 mo)	—	—	MD (DA−L-Dopa) −1.36 (−4.43 to 1.71)* / −1.36 (−4.07 to 1.34) / −0.71 (−2.03 to 0.61) / −2.28 (−8.40 to 3.85)	Figures 9, 12, 13
Yu 2025	Change in daily OFF time (h)	−1.51 ± 1.60 (n = 49)	−1.76 ± 1.70 (n = 79)	p = 0.414	Figure 9
	TEAEs / dyskinesia / non-completion	7/49 / 2/49 / 7/56	6/79 / 1/79 / 5/84	—	Figures 8, 14, 15
Haaxma 2015	Disabling fluctuations/dyskinesia (DRFD)	52% (≈26/50); median 6.1 y	60% (≈46/77); median 7.3 y	p = 0.63; dyskinesia 2.5 y later with DA (p = 0.003)	Figure 8
Chung 2018	L-Dopa-induced dyskinesia	90	90	HR 0.138 (0.024–0.785) from treatment start; 0.438 (0.105–1.832) from L-Dopa start	Figure 7
Olszewska 2022	Years from first treatment to DBS assessment / surgery	9 (IQR 4) / 10 (IQR 5)	8 (IQR 4) / 10 (IQR 5)	No significant difference	Narrative synthesis
Lanore 2025	Dyskinesia / ICRB / apathy	—	—	HR 0.48 (0.28–0.84) / 4.06 (2.48–6.67) / 0.36 (0.26–0.49); fluctuations, psychosis, sleepiness NS	Figures 7, 16

Lee 2026	5-year all-cause mortality	L-Dopa + DA (n = 1,645)	L-Dopa (n = 2,816)	ΔRMST +0.95 months (0.09–1.82) in favour of L-Dopa + DA	Narrative synthesis

Values are n/N, mean ± SD or effect estimate (95% CI). *The confidence interval for UPDRS-III in Picillo 2021 is centred on −1.36, consistent with a sign omission in the published point estimate; the CI-consistent value was used. DRFD event counts for Haaxma 2015 were back-calculated from reported percentages. EDVR, effective distribution volume ratio; ICD, impulse control disorder; ICRB, impulse control and related behaviours; NS, not significant; PDRP, Parkinson's disease-related metabolic pattern; RMST, restricted mean survival time; TEAE, treatment-emergent adverse event.

Among the six RCTs, risk of bias was judged as some concerns in four and high in two (Figures 3 and 4; Table 6). The commonest source of concern was the open-label administration of treatment, which affected deviations from intended interventions in all trials except the observer-blinded PET study, together with subjective, unblinded assessment of motor complications in CASTLE and of diary-based OFF time in the study by Yu et al. Randomisation methods were insufficiently described in three trials. PD MED had a low risk of bias for randomisation, missing data and selective reporting but some concerns regarding patient-reported outcomes collected without blinding. The two imaging RCTs had objective, quantitative primary outcomes, which mitigated the lack of participant blinding.[21]

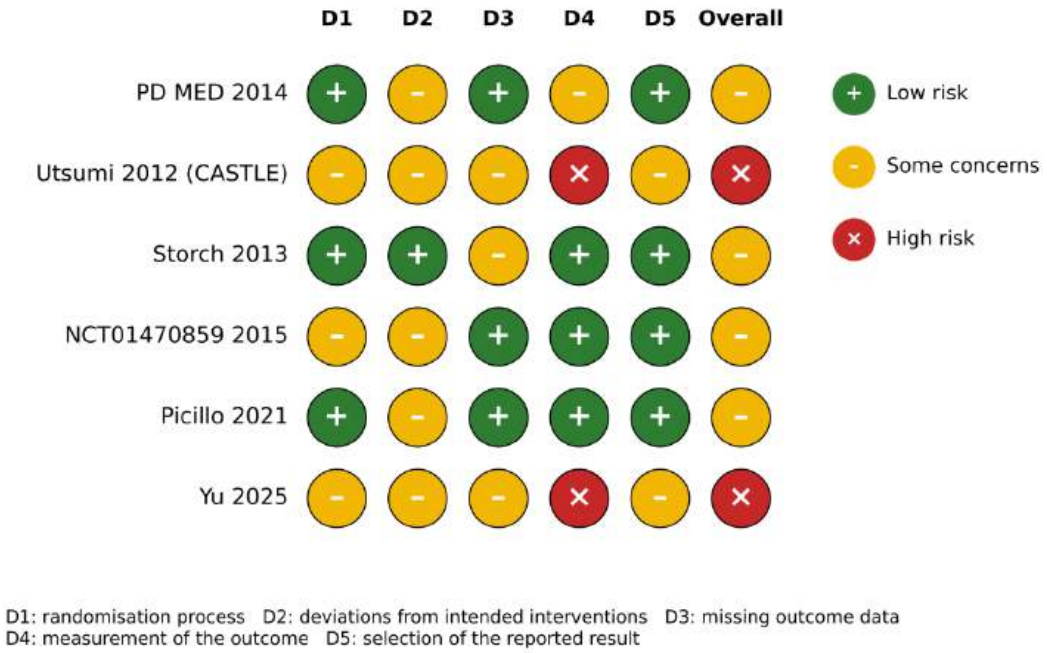


Figure 3. Risk-of-bias traffic-light plot for the randomised controlled trials (RoB 2). Green (+), low risk; yellow (–), some concerns; red (×), high risk. D1–D5 denote the five RoB 2 domains.

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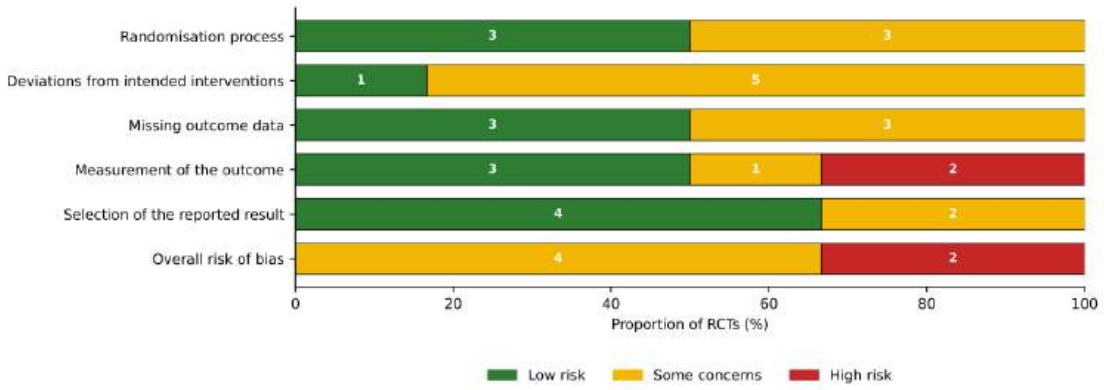


Figure 4. Summary of risk-of-bias judgements across RoB 2 domains for the six randomised controlled trials, expressed as the proportion of trials in each category; numbers within bars indicate the number of trials.

Table 6. Risk-of-bias assessment of randomised controlled trials (RoB 2) with supporting rationale

Trial	D1	D2	D3	D4	D5	Overall	Principal rationale
PD MED 2014	Low	Some	Low	Some	Low	Some concerns	Central telephone randomisation; open-label pragmatic design; unblinded patient-reported outcomes; registered (ISRCTN69812316)
Utsumi 2012	Some	Some	Some	High	Some	High	Randomisation method not reported; open-label; motor complications assessed by unblinded investigators; no registry record identified
Storch 2013	Low	Low	Some	Low	Low	Some concerns	Observer-blinded; 4 of 39 randomised participants not in primary analysis;

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							objective PET outcome
NCT01470859	Some	Some	Low	Low	Low	Some concerns	Allocation method not detailed; no masking; 29/30 completed; prespecified registry outcomes; objective FDG-PET outcome
Picillo 2021	Low	Some	Low	Low	Low	Some concerns	Computer-generated list; patients and prescribers unblinded with protocol deviations (monotherapy failure); blinded rater; registered (NCT02347059)
Yu 2025	Some	Some	Some	High	Some	High	3:2 allocation described as randomised observational study; open-label; completer analysis; diary-based OFF time

D1, randomisation process; D2, deviations from intended interventions; D3, missing outcome data; D4, measurement of the outcome; D5, selection of the reported result. "Some" denotes some concerns.

Among the five non-randomised studies, overall risk of bias was moderate in two and serious in three (Figures 5 and 6; Table 7). Confounding by indication was the dominant concern, because younger patients and those with milder disease were preferentially started on DAs, while older and more severely affected patients received L-Dopa. The DAT-matched cohort and the NS-PARK cohort mitigated this through matching on age, sex, disease duration, motor severity and baseline DAT availability or through multivariable adjustment for dopaminergic dose and severity.

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The DBS-referral cohort carried an additional serious selection bias, because inclusion was conditional on reaching the outcome of interest. Methodological quality on the Newcastle–Ottawa Scale ranged from 6 to 9 points.[22]

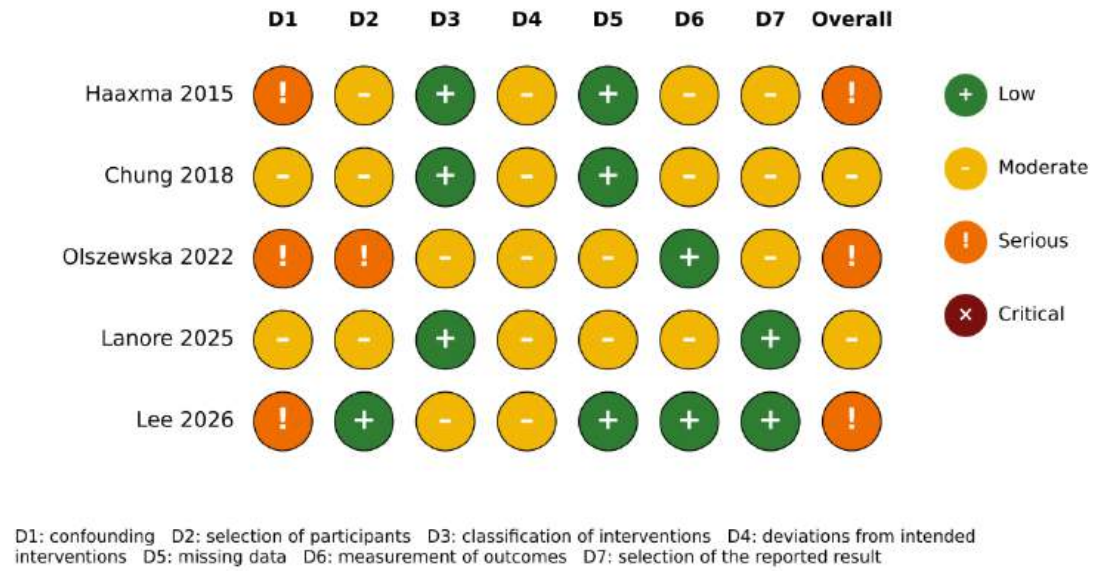


Figure 5. Risk-of-bias traffic-light plot for the non-randomised studies (ROBINS-I). Green (+), low; yellow (–), moderate; orange (!), serious; dark red (×), critical. D1–D7 denote the seven ROBINS-I domains.

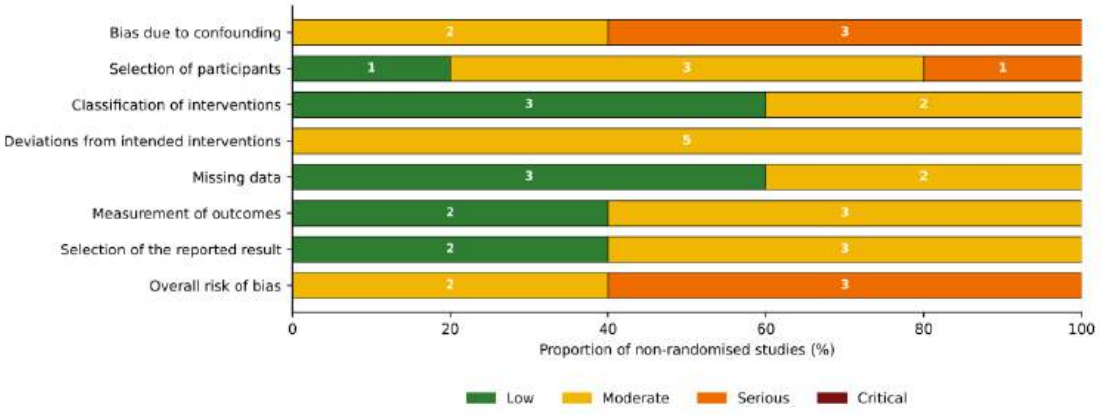


Figure 6. Summary of ROBINS-I judgements across domains for the five cohort studies, expressed as the proportion of studies in each category.

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Table 7. Risk of bias of non-randomised studies (ROBINS-I) and methodological quality (Newcastle–Ottawa Scale)

Study	D1	D2	D3	D4	D5	D6	D7	Overall	NOS (S/C/O)	NOS total
Haaxma 2015	Serious	Moderate	Low	Moderate	Low	Moderate	Moderate	Serious	3/1/3	7
Chung 2018	Moderate	Moderate	Low	Moderate	Low	Moderate	Moderate	Moderate	4/2/2	8
Olszewska 2022	Serious	Serious	Moderate	Moderate	Moderate	Low	Moderate	Serious	2/1/3	6
Lanore 2025	Moderate	Moderate	Low	Moderate	Moderate	Moderate	Low	Moderate	4/2/2	8
Lee 2026	Serious	Low	Moderate	Moderate	Low	Low	Low	Serious	4/2/3	9

D1, confounding; D2, selection of participants; D3, classification of interventions; D4, deviations from intended interventions; D5, missing data; D6, measurement of outcomes; D7, selection of the reported result. NOS, Newcastle–Ottawa Scale: S, selection (maximum 4); C, comparability (maximum 2); O, outcome (maximum 3).

Three studies (one RCT and two cohorts; approximately 1,511 participants) reported time-to-event estimates for dyskinesia or motor complications. Initiating treatment with a DA was associated with a 55% lower hazard compared with initiating L-Dopa (HR 0.45, 95% CI 0.28–0.73; $p = 0.001$), without statistical heterogeneity ($I^2 = 0\%$, $\tau^2 = 0$; $Q = 1.98$, $p = 0.37$). The NS-PARK cohort contributed 75.4% of the weight (Figure 7). When the HKSJ adjustment was applied, the interval widened to 0.16–1.28 ($p = 0.081$), and the 95% prediction interval (0.02–9.92) indicated that the direction of the effect in a future setting could not be predicted with confidence. In the

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DAT-matched cohort the protective association was strongest from the start of treatment (HR 0.138) but attenuated and lost significance once L-Dopa was added (HR 0.438, 0.105–1.832), indicating that DA-first therapy postpones rather than prevents dyskinesia.[41,48,50]

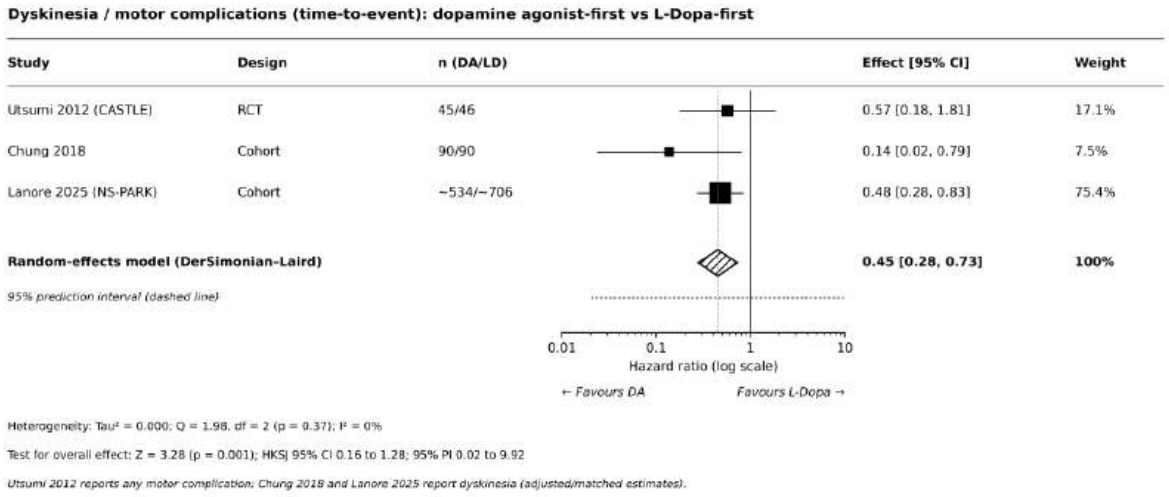


Figure 7. Forest plot of hazard ratios for dyskinesia or motor complications with DA-first versus L-Dopa-first therapy (random effects, DerSimonian–Laird). Squares are proportional to study weight; the hatched diamond denotes the pooled estimate and the dashed line the 95% prediction interval.

When motor complications were analysed as clinically relevant or disabling events, the direction favoured DAs in early PD but did not reach significance (RR 0.67, 0.31–1.44; I^2 = 55%; two studies), and the overall estimate including the wearing-off trial was RR 0.76 (0.36–1.61; I^2 = 43%; Figure 8). In the 15-year Dutch cohort, disabling response fluctuations and dyskinesia occurred in 52% of DA-starters and 60% of L-Dopa-starters, with no significant difference in risk or timing, despite dyskinesia emerging approximately 2.5 years earlier in L-Dopa-starters. The test for subgroup differences between early and fluctuating PD was not significant (Q-between = 1.53, p = 0.22). Motor-fluctuation burden, assessed as UPDRS-IV after DBS or daily OFF time in patients with wearing-off, did not differ between strategies (g −0.02, −0.48 to 0.44; I^2 = 40%; Figure 9).[45–47]

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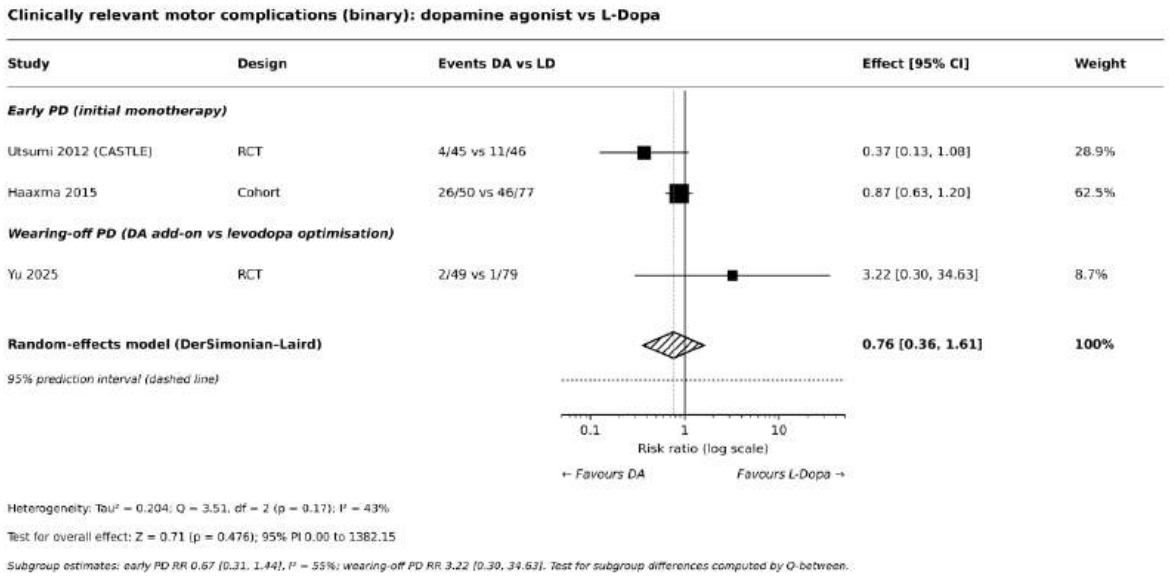


Figure 8. Forest plot of risk ratios for clinically relevant motor complications, stratified by disease stage (early PD with initial monotherapy versus fluctuating PD with DA add-on compared with L-Dopa optimisation).

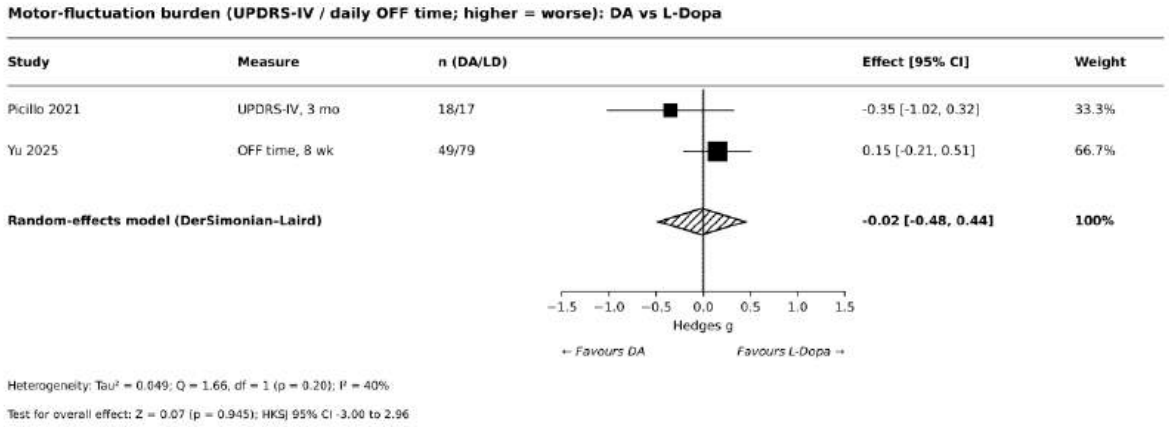


Figure 9. Forest plot of standardised mean differences in motor-fluctuation burden (UPDRS-IV after deep brain stimulation; change in daily OFF time in patients with wearing-off) with DA versus L-Dopa.

Long-term progression milestones were available from PD MED, in which 1,620 newly diagnosed patients were followed for a median of 3 years and up to 7 years. Compared with L-

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Dopa, levodopa-sparing initial therapy did not reduce the hazard of dementia (HR 1.23, 0.93–1.64), admission to institutional care (HR 1.16, 0.85–1.59) or death (HR 1.18, 0.95–1.46). In the 15-year update reported in abstract form, the dementia estimate reached nominal significance in favour of L-Dopa (HR for levodopa-sparing 1.19, 1.03–1.38), whereas mortality and institutionalisation remained similar (Figure 10). Consistently, in the DBS-referral cohort the median interval from first treatment to DBS was 10 years in both L-Dopa-first and DA-first patients, and in the Korean nationwide cohort early adjunctive DA therapy was associated with only a marginal difference in 5-year restricted mean survival time (+0.95 months, 0.09–1.82), which the authors attributed to residual confounding by frailty and severity.[43,49,51,52]

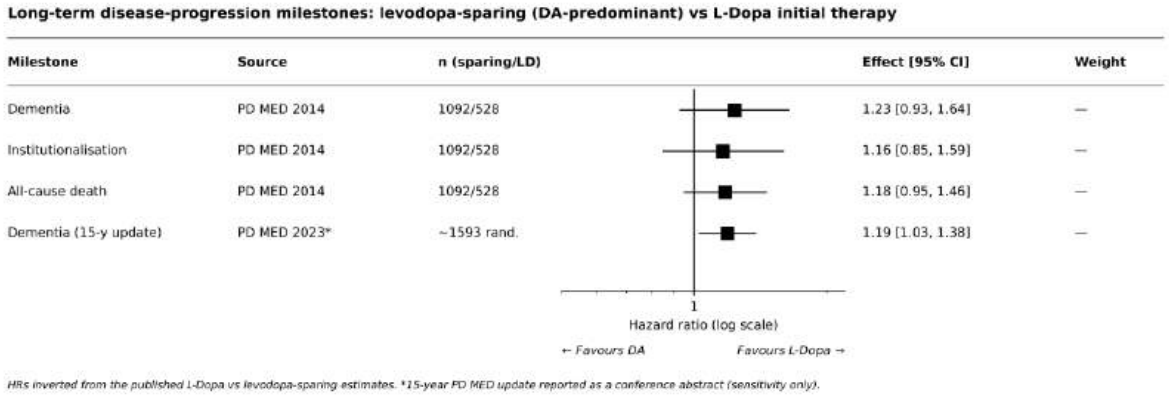


Figure 10. Long-term disease-progression milestones in the PD MED trial with levodopa-sparing (predominantly DA) versus L-Dopa initial therapy. Hazard ratios were inverted from the published L-Dopa versus levodopa-sparing contrasts; values above 1 indicate a higher hazard with levodopa-sparing therapy.

Two RCTs assessed neuroimaging markers of progression. In the 18F-DOPA PET trial, putaminal effective distribution volume ratio declined by 8.3% with L-Dopa and by 1.0% with cabergoline over 12 weeks, a non-significant between-group difference of 7.3% (−1.2% to 15.8%) that the investigators interpreted as a pharmacological increase in dopamine turnover rather than accelerated neuronal loss. In the FDG-PET trial, expression of the Parkinson's disease-related metabolic pattern increased by 0.61 Z-units with pramipexole and 0.41 Z-units with L-Dopa over 12 months ($p = 0.84$). Pooled, the standardised difference in adverse imaging change was null (g

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−0.16, −1.00 to 0.68), with moderate heterogeneity reflecting opposite directions of effect (I^2 = 65%; Figure 11).[42,44]

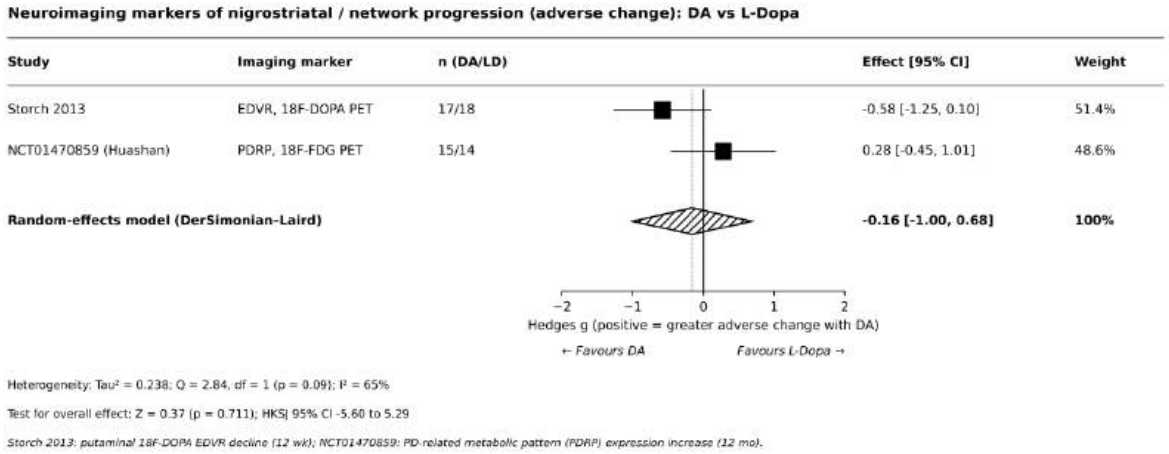


Figure 11. Forest plot of standardised mean differences (Hedges g) in neuroimaging markers of nigrostriatal and network progression. Positive values indicate greater adverse change (larger decline in 18F-DOPA uptake or larger increase in PDRP expression) with DA therapy.

Clinical progression measured by the motor examination did not differ between strategies (UPDRS-III MD −1.02, −3.77 to 1.74; I^2 = 0%), nor did progression of activities-of-daily-living disability (UPDRS-II MD 0.01, −2.50 to 2.51; I^2 = 49%; Figure 12). In the 12-month FDG-PET trial, Hoehn–Yahr stage increased by 0.39 with pramipexole and 0.30 with L-Dopa (MD 0.09, −0.26 to 0.44). In the 15-year Dutch cohort, DA-starters showed a smaller adjusted improvement in motor scores than L-Dopa-starters, consistent with the greater symptomatic potency of L-Dopa rather than with any difference in the rate of degeneration.[44,45,47]

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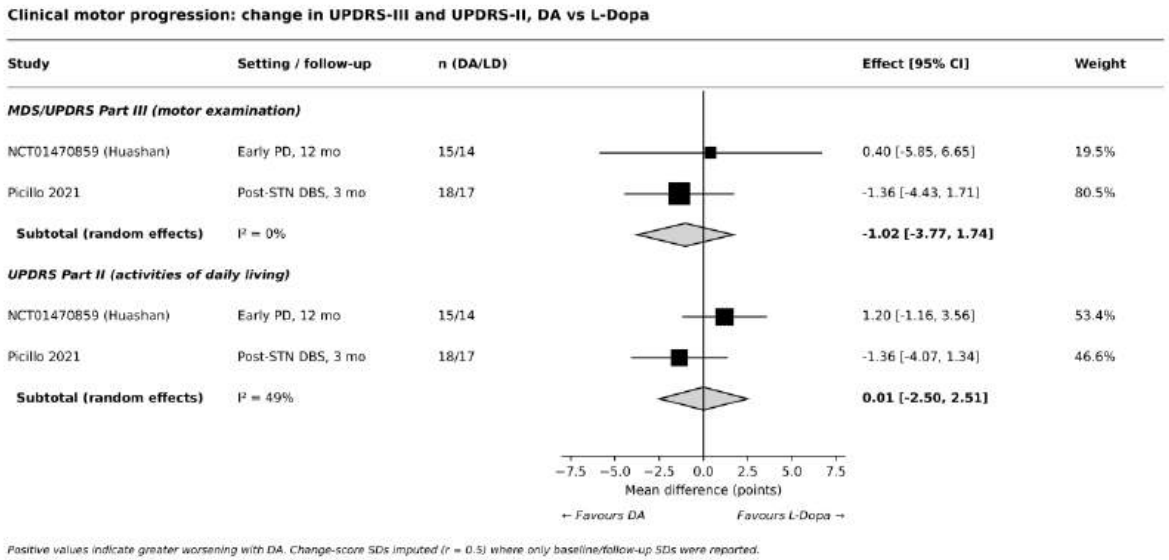


Figure 12. Forest plot of mean differences in change from baseline of UPDRS Part III (motor examination) and Part II (activities of daily living) with DA versus L-Dopa. Grey diamonds denote random-effects subtotals.

Patient-reported quality of life, available from three RCTs (1,684 participants), was slightly but significantly worse with DA-based strategies (g 0.14, 0.04–0.24; p = 0.008; I^2 = 0%; Figure 13). This finding was driven by PD MED, in which PDQ-39 mobility scores averaged 1.8 points better and EQ-5D utility 0.03 better with L-Dopa throughout 7 years of observation; the two small trials were individually inconclusive, and after exclusion of PD MED the pooled estimate was g −0.14 (−0.63 to 0.35).[43–45]

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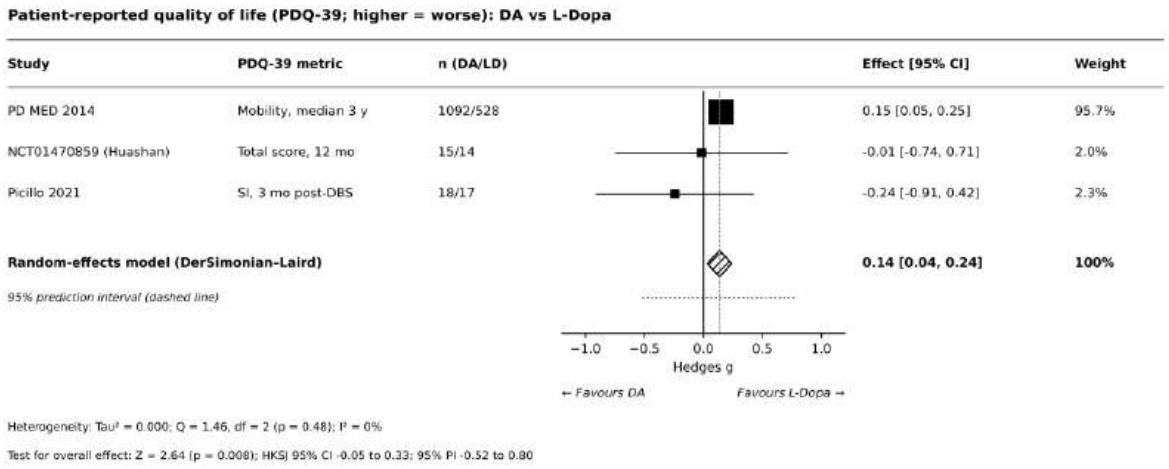


Figure 13. Forest plot of standardised mean differences in patient-reported quality of life (PDQ-39; higher scores indicate worse quality of life) with DA versus L-Dopa.

The proportion of participants experiencing any adverse event was numerically higher with DAs (RR 1.53, 0.81–2.91; I^2 = 31%; three RCTs; Figure 14). Discontinuation or failure of the allocated strategy was markedly more frequent with DAs in PD MED (28% versus 2%; RR 13.59) and in the post-DBS trial, in which 83% of patients allocated to DA monotherapy failed to maintain it at 6 months compared with 35% of those allocated to L-Dopa, and none remained on DA monotherapy at long-term follow-up compared with 47% on L-Dopa. Because of the extreme magnitude of the PD MED estimate, heterogeneity was substantial (RR 3.15, 0.88–11.33; I^2 = 86%; Figure 15); after its exclusion the remaining trials yielded a consistent and significant excess of failure with DAs (RR 2.14, 1.22–3.77; I^2 = 0%).[41,43–46]

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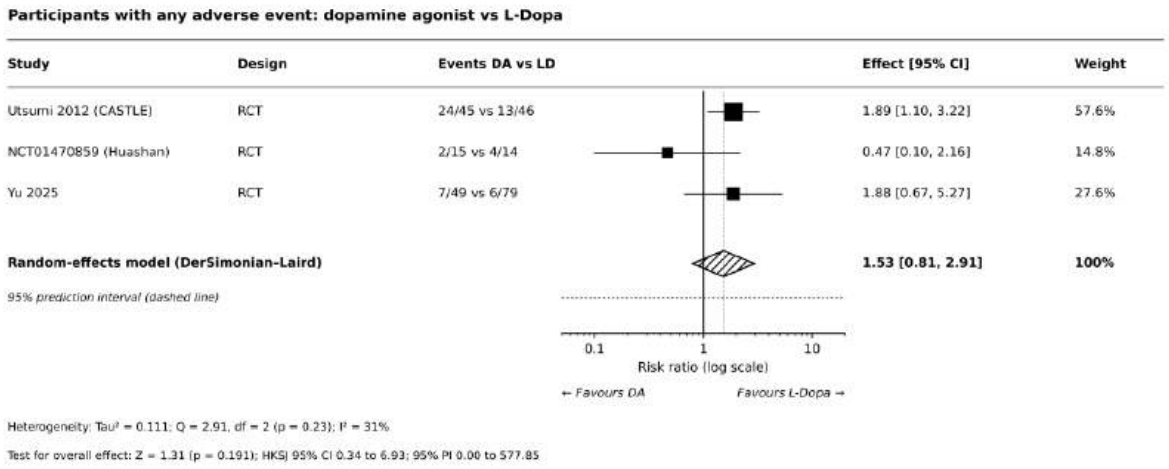


Figure 14. Forest plot of risk ratios for participants experiencing any adverse event with DA versus L-Dopa.

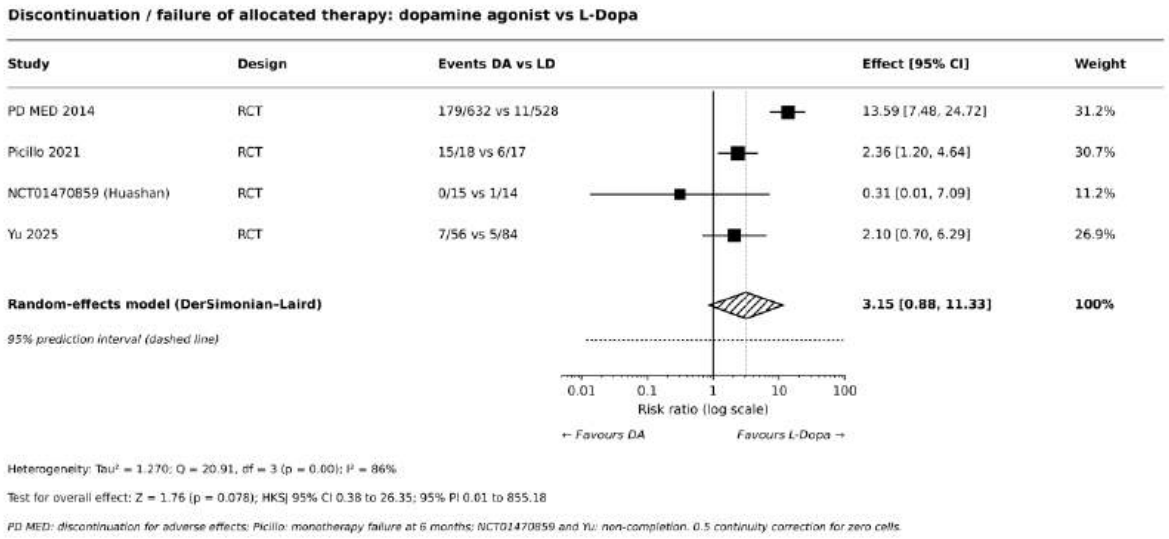


Figure 15. Forest plot of risk ratios for discontinuation or failure of the allocated therapy with DA versus L-Dopa. A continuity correction of 0.5 was applied to zero-event cells.

Impulse control and related disorders were approximately four times more frequent with DA-based strategies (pooled ratio 4.15, 2.55–6.75; $I^2 = 0\%$), driven by the adjusted NS-PARK estimate (HR 4.06) and supported by new-onset impulse control disorders in 22% of patients on DA monotherapy after DBS, compared with none on L-Dopa. Conversely, DA-based strategies were

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associated with a lower hazard of apathy in NS-PARK (HR 0.36, 0.26–0.49), although apathy scores increased more with DA monotherapy after DBS, an observation explained by the concomitant withdrawal of L-Dopa in that context. Somnolence was reported only with pramipexole in the FDG-PET trial (2/15 versus 0/14), and psychosis and daytime sleepiness did not differ in NS-PARK (Figure 16).[44,45,50]

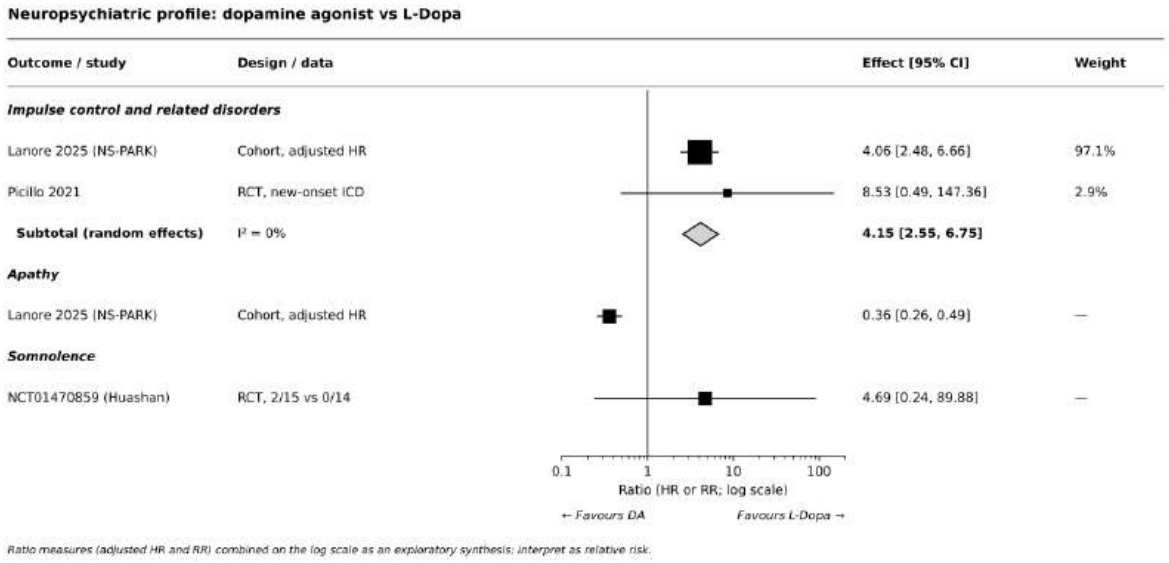


Figure 16. Forest plot of the neuropsychiatric profile of DA versus L-Dopa: impulse control and related disorders (exploratory pooling of an adjusted hazard ratio and a risk ratio), apathy and somnolence.

All pooled estimates, together with heterogeneity statistics, HKSJ-adjusted intervals and prediction intervals, are summarised in Table 8.

Table 8. Summary of pooled estimates for all quantitative syntheses (DA strategy versus L-Dopa strategy; random-effects model)

Outcome	k (design)	N	Measure	Pooled estimate (95% CI)	p	I^2 / τ^2	HKSJ 95% CI	95% PI
Dyskinesia / motor	3 (1 RCT,	≈1,511	HR	0.45 (0.28–	0.001	0% /	0.16–	0.02–

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complications (time-to-event)	2 cohorts)			0.73)		0.000	1.28	9.92
Clinically relevant motor complications (binary)	3 (2 RCT, 1 cohort)	346	RR	0.76 (0.36–1.61)	0.48	43% / 0.204	—	0.00–>100
Early PD only	2	218	RR	0.67 (0.31–1.44)	0.30	55% / 0.200	0.004–100.6	—
Neuroimaging progression marker	2 RCTs	64	Hedges g	−0.16 (−1.00 to 0.68)	0.71	65% / 0.238	−5.60 to 5.29	—
UPDRS-III change	2 RCTs	64	MD (points)	−1.02 (−3.77 to 1.74)	0.47	0% / 0.000	−9.87 to 7.84	—
UPDRS-II change	2 RCTs	64	MD (points)	0.01 (−2.50 to 2.51)	0.99	49% / 1.597	−16.22 to 16.23	—
Quality of life (PDQ-39)	3 RCTs	1,684	Hedges g	0.14 (0.04–0.24)	0.008	0% / 0.000	−0.05 to 0.33	−0.52 to 0.80
Motor-fluctuation burden	2 RCTs	163	Hedges g	−0.02 (−0.48 to 0.44)	0.95	40% / 0.049	−3.00 to 2.96	—
Any adverse event	3 RCTs	248	RR	1.53 (0.81–2.91)	0.19	31% / 0.111	0.34–6.93	0.00–>100
Discontinuation / failure of allocated	4 RCTs	1,364	RR	3.15 (0.88–11.33)	0.078	86% / 1.270	0.38–26.35	0.01–>100

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therapy								
Impulse control and related disorders	2 (1 RCT, 1 cohort)	≈1,275	Ratio	4.15 (2.55–6.75)	<0.001	0% / 0.000	—	—

Ratios below 1 and differences below 0 favour the DA strategy. HKSJ, Hartung–Knapp–Sidik–Jonkman adjustment; MD, mean difference; PI, prediction interval (calculated when k ≥ 3); k, number of studies; N, participants in the analysed arms.

Leave-one-out analyses showed that the protective association of DA-first therapy with dyskinesia persisted after omission of the RCT (HR 0.34, 0.12–1.01) or of the DAT-matched cohort (HR 0.50, 0.30–0.81), but lost statistical significance when the NS-PARK cohort was omitted (HR 0.33, 0.08–1.27), underscoring the dependence of this result on a single observational dataset (Figure 17; Table 9). For adverse events, omission of CASTLE abolished the signal (RR 1.06, 0.28–4.06), whereas for discontinuation every leave-one-out estimate remained above unity. Restriction of the dyskinesia analysis to cohort studies yielded a similar point estimate with wider uncertainty (HR 0.34, 0.12–1.01; I^2 = 44%). Cumulative meta-analysis by publication year showed that the pooled estimate stabilised with the addition of the 2025 NS-PARK data (Figure 18).

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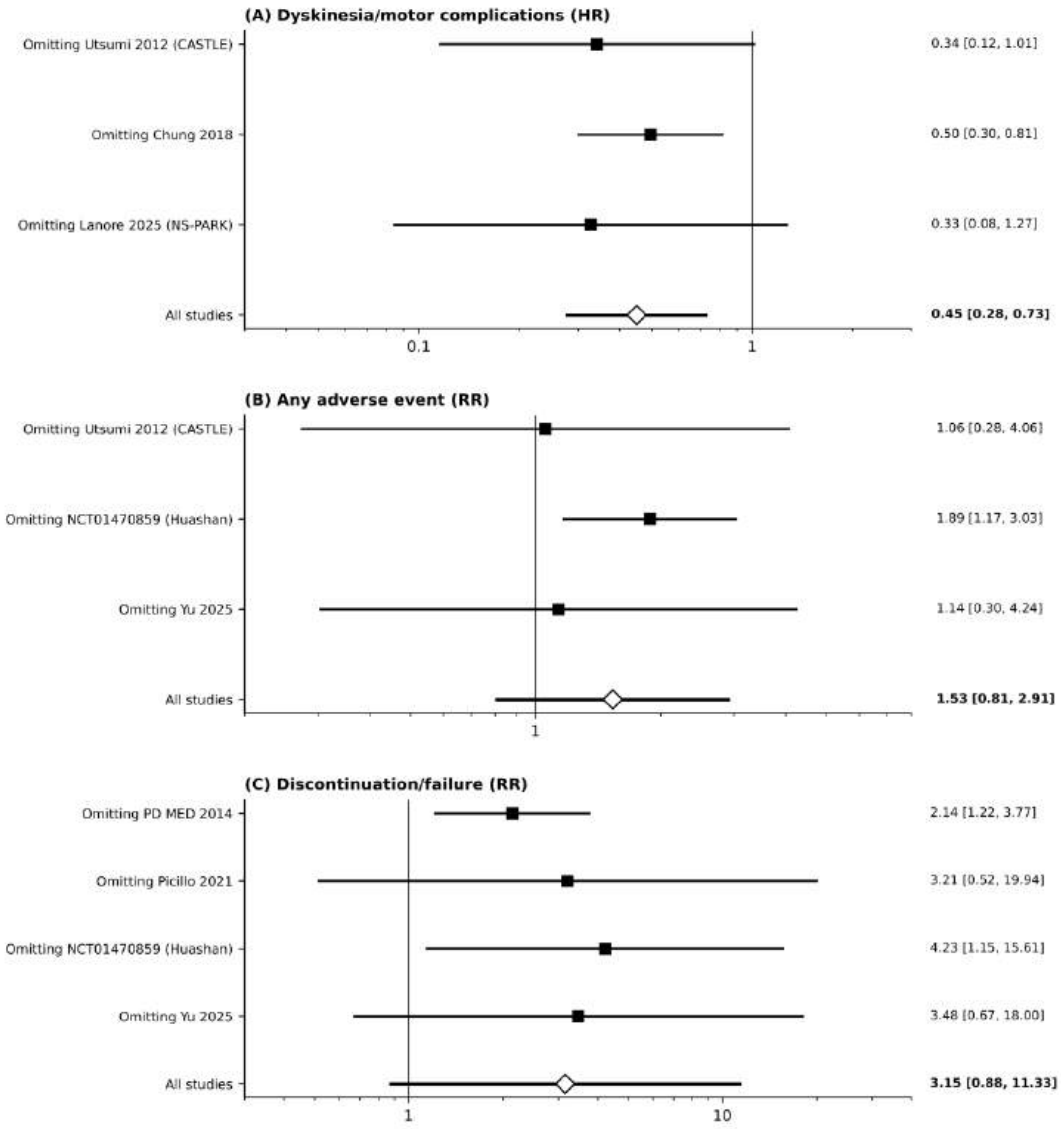


Figure 17. Leave-one-out sensitivity analyses for (A) dyskinesia or motor complications, (B) any adverse event and (C) discontinuation or failure of allocated therapy. Each row shows the pooled estimate after omission of the named study; the open diamond represents the full analysis.

Table 9. Sensitivity and subgroup analyses

Analysis	Outcome	k	Estimate (95% CI)	I^2	Interpretation

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Main analysis (DL)	Dyskinesia/MC (HR)	3	0.45 (0.28–0.73)	0%	Reference
HKSJ adjustment	Dyskinesia/MC (HR)	3	0.45 (0.16–1.28)	—	Significance lost; small-k imprecision
Omit Utsumi 2012	Dyskinesia/MC (HR)	2	0.34 (0.12–1.01)	44%	Direction preserved
Omit Chung 2018	Dyskinesia/MC (HR)	2	0.50 (0.30–0.81)	0%	Robust
Omit Lanore 2025	Dyskinesia/MC (HR)	2	0.33 (0.08–1.27)	43%	Dependent on NS-PARK
Cohorts only	Dyskinesia/MC (HR)	2	0.34 (0.12–1.01)	44%	Borderline
Early PD subgroup	Motor complications (RR)	2	0.67 (0.31–1.44)	55%	Q-between p = 0.22 vs fluctuating PD
Exclude PD MED	Quality of life (g)	2	−0.14 (−0.63 to 0.35)	0%	Signal depends on PD MED
Omit Utsumi 2012	Any adverse event (RR)	2	1.06 (0.28–4.06)	54%	Not robust
Omit NCT01470859	Any adverse event (RR)	2	1.89 (1.17–3.03)	0%	Significant excess with DA
Exclude PD MED	Discontinuation/failure (RR)	3	2.14 (1.22–3.77)	0%	Consistent excess with DA
Omit Picillo 2021	Discontinuation/failure (RR)	3	3.21 (0.52–19.94)	85%	Direction preserved
PD MED 15-year update	Dementia (HR, sparing vs L-Dopa)	1	1.19 (1.03–1.38)	—	Nominal excess with levodopa-sparing

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DL, DerSimonian–Laird; HKSJ, Hartung–Knapp–Sidik–Jonkman; MC, motor complications.

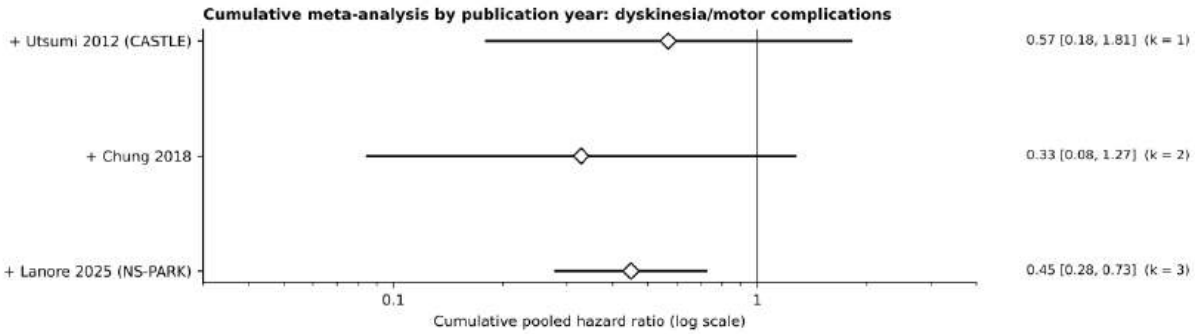


Figure 18. Cumulative meta-analysis of dyskinesia or motor complications ordered by year of publication, showing the progressive narrowing of the pooled hazard ratio.

Contour-enhanced funnel plots for the outcomes with three or more studies did not show a clear asymmetric distribution, and Egger's regression intercepts were not significant (dyskinesia p = 0.55; quality of life p = 0.28; any adverse event p = 0.41; discontinuation p = 0.39) (Figure 19). However, with three to four studies per outcome these tests have very low power and cannot exclude small-study effects. The inclusion of registry-posted results from an otherwise unpublished trial partially mitigated the risk of publication bias.[24]

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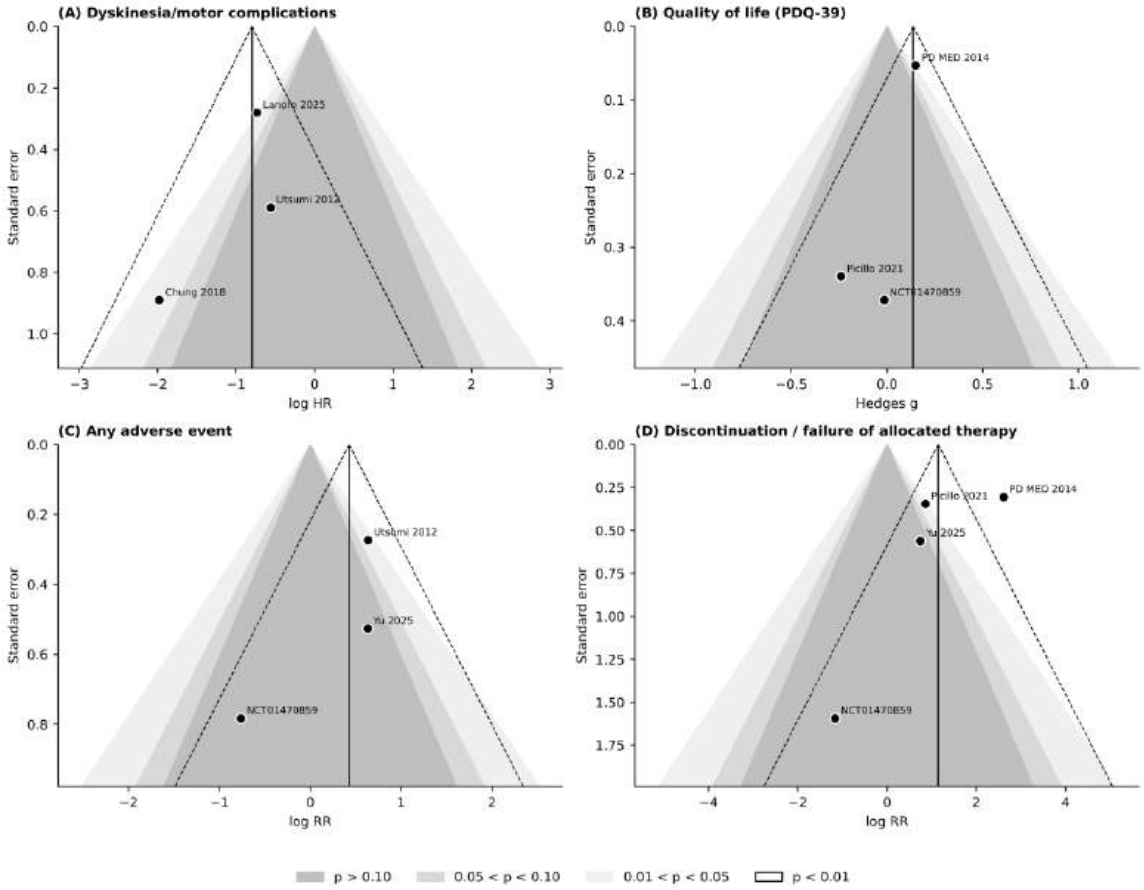


Figure 19. Contour-enhanced funnel plots for (A) dyskinesia or motor complications, (B) quality of life, (C) any adverse event and (D) discontinuation or failure of allocated therapy. Shaded regions indicate conventional significance contours around the null; the vertical line marks the pooled estimate and the dashed lines its pseudo-95% confidence limits.

A graphical overview of all pooled estimates across ratio and continuous outcomes is provided in Figure 20, illustrating that the only robust between-strategy differences concern dyskinesia timing, tolerability, neuropsychiatric safety and quality of life, and not markers of neurodegeneration.

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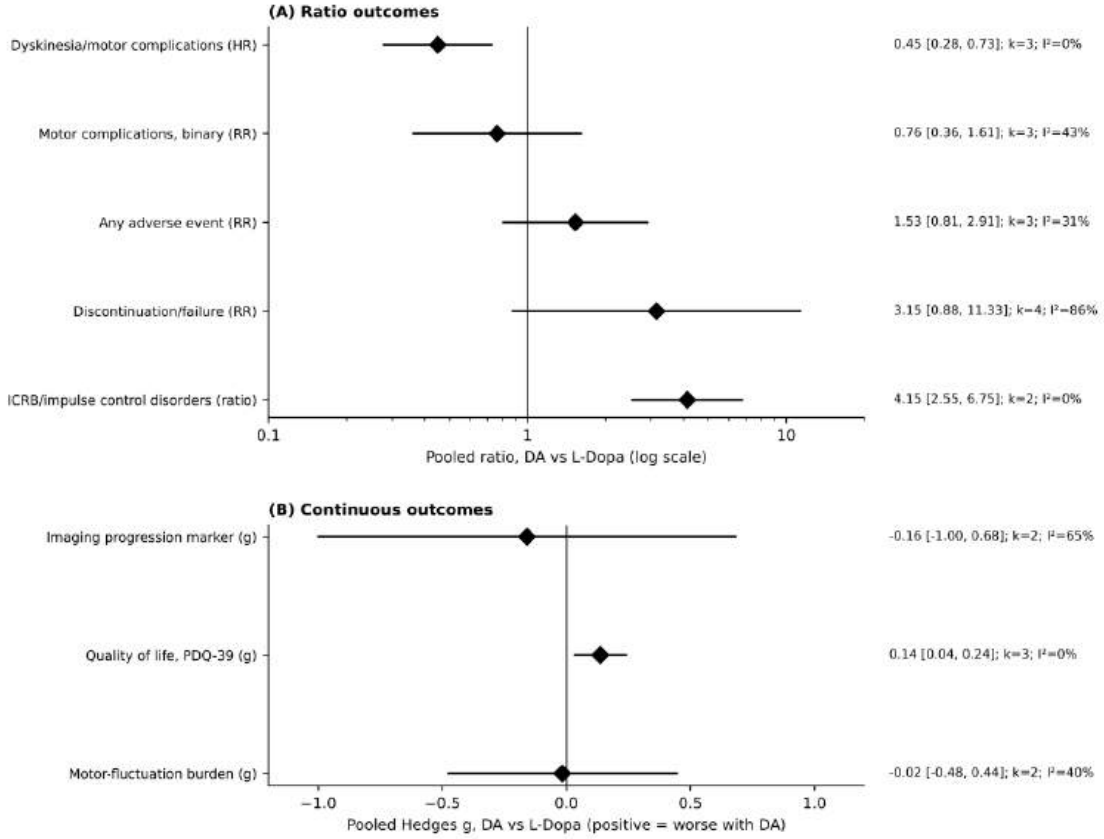


Figure 20. Overview of pooled estimates across all quantitative syntheses. (A) Ratio outcomes (values below 1 favour DA); (B) continuous outcomes expressed as Hedges g (positive values indicate a worse outcome with DA).

The narratively synthesised progression outcomes that could not be pooled are summarised in Table 10. Taken together, they indicate that DA-first therapy shifts the timing of dyskinesia but not the time to disabling motor complications, to DBS or to death, and that L-Dopa-related imaging changes in early disease reflect pharmacological regulation of dopamine turnover. The certainty of evidence according to GRADE is presented in Table 11 and ranged from very low for imaging and clinical progression markers to moderate for quality of life.[25,42,47,49,51]

Table 10. Narrative synthesis of progression-related outcomes not amenable to pooling

Domain	Study	Key finding	Direction

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Time to device-aided therapy	Olszewska 2022	Median 10 years from first treatment to DBS in both L-Dopa-first (n = 312) and DA-first (n = 126) patients; time to DBS assessment 8 vs 9 years	No difference
Survival	Lee 2026	Early adjunctive DA with L-Dopa vs L-Dopa alone: ΔRMST +0.95 months over 5 years; MAO-B inhibitor +3.45 months; confounding by frailty acknowledged	Marginal, likely confounded
Disabling motor complications	Haaxma 2015	DRFD 52% vs 60% over a median of 8.1 years; dyskinesia 2.5 y later and fluctuations 0.8 y later with DA, but similar time to disability	Delay without prevention
Dyskinesia after L-Dopa addition	Chung 2018	Protective HR 0.138 from treatment start attenuated to 0.438 (NS) once L-Dopa was introduced	Delay without prevention
Motor fluctuations	Lanore 2025	No significant difference between L-Dopa-alternative therapy and L-Dopa monotherapy after adjustment for dose and severity	No difference
Treatment sustainability	Picillo 2021	DA monotherapy after DBS: median time to failure 7.4 vs 47.8 months; 0% vs 47% maintained at ~2.5 y	Favours L-Dopa
Dopamine turnover	Storch 2013	L-Dopa increased putaminal dopamine turnover (EDVR −8.3%) vs cabergoline (−1.0%); interpreted as compensatory pharmacological effect	Pharmacological, not degenerative
Quality of life	PD MED	PDQ-39 mobility 1.8 points and EQ-5D	Favours L-Dopa

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over time	2014	0.03 better with L-Dopa, without attrition of benefit over 7 years	

DBS, deep brain stimulation; DRFD, disabling response fluctuations and dyskinesia; EDVR, effective distribution volume ratio; NS, not significant; RMST, restricted mean survival time.

Table 11. Certainty of evidence (GRADE) for the principal outcomes

Outcome	**Studies**	**Effect (95% CI)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Certainty**
Dyskinesia / motor complications	1 RCT, 2 cohorts	HR 0.45 (0.28–0.73)	Serious	Not serious	Not serious	Serious (HKSJ crosses 1)	Undetected	Low
Dementia, institutionalisation, death	1 RCT	HR 1.23 / 1.16 / 1.18	Not serious	NA (single trial)	Serious (MAO-BI in sparing arm)	Serious	Undetected	Low
Neuroimaging progression markers	2 RCTs	g −0.16 (−1.00 to 0.68)	Serious	Serious	Serious (surrogate)	Very serious	Undetected	Very low
UPDRS-III / UPDRS-II progression	2 RCTs	MD −1.02 / 0.01	Serious	Not serious	Serious (post-DBS population)	Very serious	Undetected	Very low

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Quality of life (PDQ-39)	3 RCTs	g 0.14 (0.04–0.24)	Serious (open-label)	Not serious	Not serious	Not serious	Undetected	Moderate
Any adverse event	3 RCTs	RR 1.53 (0.81–2.91)	Serious	Not serious	Not serious	Serious	Undetected	Low
Discontinuation / failure	4 RCTs	RR 3.15 (0.88–11.33)	Serious	Serious (I^2 = 86%)	Not serious	Not serious*	Undetected	Low
Impulse control and related disorders	1 RCT, 1 cohort	Ratio 4.15 (2.55–6.75)	Serious	Not serious	Not serious	Not serious	Undetected	Low (upgraded for large effect)

*All individual trials except the smallest showed an excess of failure with DAs, and the analysis excluding PD MED was precise (RR 2.14, 1.22–3.77). Certainty for non-randomised evidence was assessed with ROBINS-I-based GRADE. NA, not applicable.

DISCUSSION

This systematic review and meta-analysis of six RCTs and five cohort studies published within the last 15 years found no evidence that the initial choice between L-Dopa and a DA modifies the biological progression of Parkinson's disease. Neuroimaging markers of nigrostriatal and network degeneration, clinical progression of motor signs and disability, and hard long-term milestones (dementia, institutionalisation, need for DBS and death) did not differ in a direction compatible with DA-mediated neuroprotection or L-Dopa-mediated neurotoxicity. The single consistent benefit of DA-first therapy was a delay in the emergence of dyskinesia, which was offset

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by poorer tolerability, a higher rate of failure of the allocated strategy, a four-fold excess of impulse control and related disorders and slightly worse patient-reported quality of life.[42–44,50]

The absence of a disease-modifying signal in the present synthesis is concordant with the two most rigorous delayed-start trials conducted within the review period. In LEAP, patients randomised to early L-Dopa and those in whom L-Dopa was delayed by 40 weeks had similar UPDRS scores at 80 weeks, indicating neither a disease-modifying benefit nor a deleterious effect of early L-Dopa exposure. In PROUD, early versus delayed pramipexole produced no difference in UPDRS change or in DAT SPECT decline at 15 months. These designs, which separate symptomatic from disease-modifying effects, therefore converge with our head-to-head data in refuting the clinical relevance of the historical toxicity and neuroprotection hypotheses.[6,7,12,13]

A key explanation for the earlier divergence of imaging findings between L-Dopa and DAs, which predated the present review window, is that the surrogate markers used to infer neurodegeneration are themselves pharmacologically regulated. In the included 18F-DOPA PET trial, L-Dopa increased putaminal dopamine turnover within 12 weeks, an adaptive presynaptic response rather than accelerated cell loss. In a 6-hydroxydopamine mouse model, both L-Dopa and pramipexole modified FP-CIT binding and tyrosine hydroxylase expression in intact animals, yet neither altered the stably reduced signal or the number of nigral dopaminergic neurons in lesioned animals. DAs also down-regulate DAT expression in peripheral lymphocytes and, with chronic exposure, alter striatal D2 receptor availability. Longitudinal PPMI data further show that DAT imaging declines non-linearly in early PD. Collectively, these observations indicate that drug-induced regulation of transporter and decarboxylase expression can masquerade as differential progression, and that imaging endpoints must be interpreted with this pharmacological confound in mind.[15,26,35,36,42]

The reduction in dyskinesia hazard with DA-first therapy (HR 0.45) is biologically plausible and quantitatively consistent with earlier trial-based evidence, but our data refine its interpretation. In the DAT-matched cohort the protective association weakened substantially once L-Dopa was introduced, and in the 15-year Dutch cohort dyskinesia appeared later in DA-starters, yet the risk and time to disabling motor complications were similar. This pattern fits current pathophysiological

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models in which levodopa-induced dyskinesia results from pulsatile stimulation of denervated striatal receptors, loss of presynaptic buffering and serotonergic false-transmitter release, and depends primarily on disease duration, degree of denervation, L-Dopa dose, younger age at onset, female sex and low body weight. The observation from sub-Saharan Africa that motor complications track disease duration rather than the duration of L-Dopa exposure, together with population-based and inception-cohort data, reinforces that dyskinesia is a marker of disease stage interacting with dopaminergic dosing rather than evidence of L-Dopa-driven progression.[9,10,14,47,48,53–55]

The long-term outcomes of PD MED are particularly informative because they capture the downstream consequences of initial treatment choice in an unselected population. Levodopa-sparing therapy did not reduce dementia, institutionalisation or mortality over 7 years, and the 15-year update suggested, if anything, a modest excess of dementia with levodopa-sparing therapy, while patient-rated mobility and utility remained persistently better with L-Dopa. The absence of a difference in time to DBS in a large referral cohort, and the marginal and probably confounded survival difference in the Korean nationwide cohort, are consistent with these findings. These data challenge the residual "levodopa phobia" that continues to delay adequate symptomatic treatment in clinical practice.[11,43,49,51,52]

The neuropsychiatric profile was the most clearly divergent safety domain. The four-fold excess of impulse control and related disorders with DA-based strategies, derived largely from an adjusted analysis of a large multicentre cohort and supported by new-onset impulse control disorders in more than one-fifth of patients on DA monotherapy after DBS, accords with the cumulative, dose-dependent incidence of these disorders observed in longitudinal cohorts. The lower risk of apathy with DAs in early disease is the mirror image of this hyperdopaminergic behavioural profile and is consistent with the stimulation of mesolimbic D3 receptors. These neuropsychiatric effects, together with the much higher rate of discontinuation for adverse effects, constitute the principal clinical cost of a levodopa-sparing strategy.[45,50,56,57]

Six systematic reviews and meta-analyses identified during screening were not included in the characteristics table but were appraised to contextualise our findings (Table 12). Earlier

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syntheses of RCTs consistently showed lower odds of dyskinesia with DA monotherapy or non-ergot DAs than with L-Dopa, superior motor efficacy with L-Dopa and higher withdrawal rates on levodopa-sparing therapy. A 2024 meta-analysis of early versus delayed L-Dopa found that delaying L-Dopa did not prevent motor complications, and a 2025 meta-analysis of bromocriptine reproduced the dyskinesia advantage of DAs. None of these reviews assessed imaging or clinical progression markers or long-term disease milestones as primary outcomes, and most were confined to trials conducted before 2011. The present review complements them by focusing on progression-related endpoints, by integrating contemporary real-world cohorts and registry results and by applying small-sample corrections and GRADE.[58–63]

Table 12. Comparison with systematic reviews and meta-analyses identified during screening (not included in the quantitative synthesis)

Review (ref.)	**Scope**	**Principal findings**	**Concordance with present review**
Chondrogiorgi 2014[58]	Meta-analysis of L-Dopa-controlled RCTs of DA monotherapy in early PD	Dyskinesia OR 0.13 (0.09–0.19) with DA; risk independent of DA dose and treatment duration; dose-related effect of adjunct L-Dopa	Concordant on dyskinesia delay; no progression outcomes assessed
Xie 2015[59]	11 RCTs; L-Dopa alone vs levodopa-sparing initial therapy	Better UPDRS I–III with L-Dopa; dyskinesia RR 1.88 and wearing-off RR 1.36 with L-Dopa; discontinuation for adverse events 43.7% vs 15.8% on sparing therapy	Concordant on efficacy, complications and tolerability
Wu 2022[60]	RCTs of non-ergot DAs in early PD	Dyskinesia OR 0.21 (NEDA vs L-Dopa) and 0.31 (NEDA + open L-Dopa vs L-Dopa); risk	Concordant; supports delay rather than prevention

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		increased with L-Dopa dose in the DA group	
Zhang 2023[61]	Network meta-analysis, 9 RCTs, 2,112 patients	L-Dopa ranked highest for dyskinesia risk but best for UPDRS-II/III improvement; pramipexole least wearing-off	Concordant on efficacy–complication trade-off
Ramanzini 2024[62]	7 studies, 1,149 patients; early vs delayed L-Dopa	No difference in motor complications (OR 1.39) or dyskinesia (OR 1.52); fewer fluctuations with early start (OR 0.70); DA subgroup dyskinesia OR 1.82	Concordant: delaying L-Dopa does not alter long-term course
Afshar 2025[63]	12 RCTs, 4,060 patients; bromocriptine vs L-Dopa and others	Dyskinesia OR 0.50 (0.31–0.80) with bromocriptine; UPDRS SMD 0.18 (−0.03 to 0.39)	Concordant on dyskinesia; no disease-modification outcomes

NEDA, non-ergot dopamine agonist; OR, odds ratio; RR, risk ratio; SMD, standardised mean difference.

From a clinical perspective, these findings support current guideline recommendations that L-Dopa is an appropriate first-line therapy at any age when symptoms impair function, and that a DA may reasonably be chosen for younger patients with mild symptoms who place a high value on postponing dyskinesia, provided that they are counselled and monitored for impulse control disorders, somnolence and oedema. Crucially, neither choice should be presented to patients as neuroprotective. The selection of initial therapy should therefore be framed as a symptomatic trade-off between earlier dyskinesia with L-Dopa and a higher burden of non-motor and behavioural adverse effects with DAs, while disease-modifying interventions remain an unmet need.[2,8,16–18]

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This review has several strengths. It was restricted to contemporary evidence published within the last 15 years, integrated randomised and real-world comparative data, retrieved unpublished registry results to mitigate publication bias, used outcome-specific risk-of-bias tools, applied the HKSJ adjustment and prediction intervals appropriate for small numbers of studies, and graded the certainty of every principal outcome. All effect sizes were oriented consistently and inverted where necessary, and sensitivity analyses tested the dependence of each conclusion on individual studies.[23,25]

Future research should evaluate progression with outcomes that are not confounded by dopaminergic regulation, such as practically defined OFF-medication examinations, neuromelanin-sensitive and diffusion imaging, and biological markers of α-synuclein pathology, within long-term pragmatic randomised designs or individual-participant-data analyses of large longitudinal cohorts. Delayed-start and treatment-withdrawal designs remain the most informative approaches for separating symptomatic from disease-modifying effects, and core outcome sets that include patient-reported quality of life, neuropsychiatric safety and hard milestones should be harmonised across studies.[7,12,15]

CONCLUSION

Contemporary randomised and real-world evidence does not support a neuroprotective advantage of dopamine agonists over L-Dopa, nor a neurotoxic effect of L-Dopa, on the progression pattern of Parkinson's disease. Initiating treatment with a dopamine agonist delays the onset of dyskinesia but does not prevent disabling motor complications and does not alter imaging or clinical markers of progression, the time to device-aided therapy, dementia, institutionalisation or survival. This delay is purchased at the cost of higher rates of treatment failure and discontinuation, impulse control and related disorders and marginally worse quality of life. The choice of initial dopaminergic therapy should therefore be individualised on symptomatic and safety grounds, and the certainty of the evidence for progression-related outcomes, which is low to very low, warrants long-term trials using pharmacologically insensitive markers of neurodegeneration.[16,43,50]

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DECLARATIONS

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