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Advances in neurological therapies: A review of clinical trials in Alzheimer's, Parkinson's, and multiple sclerosis

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ABSTRACT

The period from 2020 to 2025 marked a pivotal juncture in the treatment of major neurological diseases, with Phase II–IV trials delivering the first compelling evidence for disease-modifying interventions in Alzheimer's disease, Parkinson's disease, and multiple sclerosis. This narrative review provides a critical analysis of this evolving therapeutic landscape, focusing on efficacy, safety, and practical implications. Our analysis reveals unprecedented yet heterogeneous progress. In Alzheimer's disease, anti-amyloid monoclonal antibodies (donanemab, lecanemab) achieved regulatory approval, establishing a new treatment paradigm despite modest efficacy and risks of amyloid-related imaging abnormalities (ARIA). In Parkinson's disease, GLP-1 receptor agonists (lixisenatide) demonstrated the first convincing disease modification signals in Phase II trials. For multiple sclerosis, the failure of Bruton's tyrosine kinase (BTK) inhibitors contrasted with the consolidation of anti-CD20 therapies as the therapeutic standard, refined by innovations in dosing and delivery. Collectively, these findings herald a new era of disease-modifying therapy in neurology, though current gains remain limited and dependent on biomarker stratification and safety monitoring. The challenge ahead is translating these successes into accessible, sustainable clinical benefits.

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Introduction

Chronic neurological diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS), represent leading causes of disability and premature mortality worldwide, exerting an escalating and unsustainable burden on health systems.[1,2,3] Alzheimer's disease alone affects over 55 million people globally, with projections exceeding 139 million by 2050.[4] Parkinson's disease is the fastest-growing neurological condition in prevalence, currently affecting more than 8.5 million individuals,[5] while multiple sclerosis remains the most common cause of non-traumatic neurological disability in young adults, impacting approximately 2.8 million people worldwide, with rising incidence even in traditionally low-prevalence regions.[6,7]

Despite significant advances in the understanding of pathophysiological mechanisms, interventions with a meaningful impact on the natural history of these diseases remain limited.[8,9] In Alzheimer's disease, successive anti-amyloid

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and anti-tau strategies have failed to achieve consistent clinical benefits, raising doubts about the amyloid hypothesis.[10,11] In Parkinson's disease, multiple attempts at neuroprotection have yielded inconclusive results, leaving dopaminergic replacement as the cornerstone of symptomatic therapy.[12,13,14] Similarly, in multiple sclerosis, although disease-modifying therapies (DMTs) have revolutionized the management of relapsing-remitting forms, progressive multiple sclerosis remains largely refractory to treatment, underscored by a series of negative clinical trials.[15,16]

This therapeutic imbalance is reflected in current clinical practice. Until recently, Alzheimer's disease management was restricted to symptomatic agents such as acetylcholinesterase inhibitors and memantine, with minimal effect on disease progression.[17,18] In Parkinson's disease, therapeutic strategies continue to revolve around dopaminergic agents and adjuvants that alleviate symptoms without altering the course of neurodegeneration.[19,20] For multiple sclerosis, the past decade has expanded the therapeutic arsenal for relapsing-remitting disease through oral immunomodulators and monoclonal antibodies, yet effective interventions for progressive forms remain elusive.[21,22] These limitations have stimulated a new wave of clinical trials aimed both at validating traditional mechanistic hypotheses and at testing novel biological targets.

Notably, while the literature is replete with systematic reviews in clinical neuroscience, most synthesize preclinical evidence alongside observational studies, which weakens the ability to critically evaluate the strength of clinical data.[23,24] There is a clear gap for analyses focused specifically on Phase II–IV interventional trials for new therapies, which represent the translational bridge from discovery to clinical implementation.

The period between 2020 and 2025 can thus be regarded as a pivotal transitional phase. During these years, large-scale clinical trials have tested candidate therapies with the explicit goal of modifying disease trajectories, marking a potential turning point in the management of Alzheimer's disease, Parkinson's disease, and multiple sclerosis.[25,26,27]

The present review aims to provide a critical synthesis of Phase II–IV clinical trials conducted between 2020 and 2025, focusing specifically on therapeutic interventions for Alzheimer's disease, Parkinson's disease, and multiple sclerosis. We highlight not only the magnitude of efficacy and safety outcomes but also the limitations, clinical implications, and barriers to implementing these emerging therapies. By contextualizing the scope and impact of these advances, this review seeks to clarify their true relevance for the development of future treatments and the evolving landscape of modern neurology.

CLINICAL SIGNIFICANCE

- Recent clinical trials have provided the first evidence of disease-modifying effects in major neurological disorders.
- Anti-amyloid antibodies for Alzheimer's, GLP-1 agonists for Parkinson's, and anti-CD20 therapies for multiple sclerosis mark distinct advances in treatment.
- These findings highlight a shift toward precision and biomarker-guided therapies with tangible clinical implications.
- Despite progress, accessibility, safety, and real-world applicability remain central clinical challenges.

Mechanistic foundations guiding clinical development

Therapeutic progress in neurological diseases depends on an integrated understanding of pathophysiology, which informs target selection and clinical trial design.[28] Although clinically distinct, Alzheimer's disease, Parkinson's disease, and multiple sclerosis share chronic, multifactorial, and progressive courses. Recent advances largely stem from the maturation of biological hypotheses developed over past decades.[26,27]

In Alzheimer's disease, core pathogenic processes include extracellular amyloid-β (Aβ) accumulation and intracellular hyperphosphorylated tau, driving synaptic loss and cognitive decline. Aβ42/40 peptides produced by APP cleavage (BACE1, γ-secretase) disrupt synaptic homeostasis via aberrant NMDAR/Fyn signaling, calcium overload, and oxidative stress.[29] Hyperphosphorylated tau (GSK3β, CDK5) impairs axonal transport and propagates trans-synaptically. Microglial activation (TREM2), astrogliosis, complement pathways, and blood–brain barrier/glymphatic dysfunction exacerbate protein deposition. Pathology spreads from the entorhinal cortex/hippocampus to association cortices, paralleling the progression from episodic memory loss to executive and visuospatial impairment.[30] Biomarkers reflect these processes: CSF/plasma Aβ42/40 and amyloid PET (Aβ burden); p-tau217/231 and tau PET (tau spread); GFAP (astrogliosis); NfL (axonal injury).[31]

In Parkinson's disease, selective dopaminergic loss in the substantia nigra pars compacta causes striatal dopamine depletion and motor symptoms.[32 -24] Vulnerability relates to Ca^{2+}-dependent pacemaking (Cav1.3), elevated oxidative metabolism, and mitochondria-associated membrane stress, leading to oxidative injury, complex I dysfunction, and impaired mitophagy (PINK1/Parkin) (Filidei et al., 2025). Misfolded α-synuclein aggregates spread trans-synaptically and induce synaptic toxicity. Autophagy–lysosome dysfunction (GBA1, RAB proteins) and microglial activation amplify neurodegeneration.[33] Non-motor prodromes—REM sleep behavior disorder, hyposmia, constipation, mood changes—often precede motor features, which emerge after ~50–60% dopaminergic denervation. Progression involves cholinergic and serotonergic systems,

contributing to postural instability, cognitive decline, and autonomic dysfunction.[34,35] Biomarkers include CSF/plasma NfL, α-synuclein seeding assays, and digital markers of sleep and autonomic function.[36]

In multiple sclerosis, loss of immune tolerance triggers Th1/Th17 and B-cell activation, BBB disruption (VCAM-1, MMPs), and inflammatory demyelination with axonal injury.[37] Chronic inflammation is maintained by microglia, complement activation, and cytokines. Progressive disease features compartmentalized pathology: meningeal B-cell aggregates, iron-rim "smoldering" lesions, and impaired oligodendrocyte precursor differentiation, leading to cortical atrophy.[23,24] Clinically, MS reflects interactions between acute relapses and chronic progression, influenced by age at onset and individual trajectories. MRI (T2, enhancing lesions, iron rims), serum NfL, and atrophy/network metrics track disease activity.[38]

Clinical advances in Alzheimer's disease show modest benefits

From 2020 to 2025, Phase III trials centered on amyloid-targeting antibodies, with limited but unprecedented disease-modifying effects Table 1.

Donanemab (TRAILBLAZER-ALZ 2): In 1,736 early AD patients with low−intermediate tau, 76 weeks of treatment slowed decline by 35.1% on the iADRS (−3.25 points; $P < 0.001$) and reduced CDR-SB by 0.7 points. ARIA occurred in 24% of treated patients (vs. 2.1% placebo), with 6% symptomatic and 3 fatal cases.[39,40]

Lecanemab (CLARITY-AD): In 1,795 early AD patients, 18 months of treatment reduced CDR-SB decline by 27% (−0.45 points; $P < 0.001$)17. ARIA-E occurred in 12.6%, restricting use to specialized centers.[41,42]

Solanezumab (A4): No cognitive benefit despite biomarker changes, emphasizing that only potent plaque- and protofibril-clearing antibodies yield clinical effects.[40,43]

Non-amyloid approaches

GV-971 improved ADAS-Cog12 by −2.15 points at 36 weeks ($P < 0.0001$) in 818 patients but failed secondary endpoints.[44,45] Tilavonemab (anti-tau) failed;[46] AR1001 (PDE5 inhibitor) shows preliminary benefit; simufilam remains controversial; semaglutide is being tested in the EVOKE/EVOKE+ trials (>1,800 participants each).[47]

Biomarker progress has been substantial. Plasma GFAP discriminates amyloid positivity with AUC 0.86, sometimes

Table 1 Advances in Alzheimer's disease (2020−2025): clinical trials and translational perspectives.

NCT	Intervention	Phase	n	Primary endpoint	Main results	Safety
NCT04437511	Donanemabe (anti-β-amyloid) vs. placebo	III	1.736	iADRS (76s) / CDR-SB	iADRS: +3.25 points (P<0.001, ~35% slowdown); CDR-SB: −0.70 points (P<0.001)	ARIA-E 24% (6.1 % symptomatic) vs. 2.1% placebo; ARIA-H 31% vs. 13%
NCT04520412	GV-971 (Sodium oligomeric) vs. placebo	III	818	ADAS-Cog12 (36s)	Δ −2.15 points (95% CI −3.07 to −1.23; P<0.0001)	TEAE ~74% in both; well tolerated
NCT04468659	Lecanemab (AHEAD 3-45, early prevention) vs. placebo	III	1.400	CDR-SB (in progress)	Results not yet published; approved by the FDA in 2023 in another cohort	ARIA-E ~12% in earlier studies
NCT05531526	AR1001 (PDE5 inhibitor) vs. placebo	III	1.535	ADAS-Cog, CDR-SB (Polaris-AD)	Pending results	Preliminary data indicate good tolerability
NCT05575076	Simufilam (filamentous filament binder)	III (extension)	1.081	Cognition (ADAS-Cog)	Scientific controversy; definitive results pending	Security profile deemed acceptable
NCT04777409 / NCT04777396	Semaglutide (GLP-1 RA, EVOKE/EVOKE +) vs. placebo	III	1.840 cada	CDR-SB (104s)	In progress	Safety compatible with GLP-1 (nausea, vomiting)

Major Phase III/IV and Phase II trials selected for clinical relevance. Columns include: NCT, intervention/class, phase, sample (n), primary endpoint (with time of assessment), primary outcome (metric, effect, 95% CI, p when available), and safety (adverse events of interest, e.g., ARIA). Trials with unpublished data are identified as "not available/pending." Notes: When multiple primary endpoints exist, the functional/cognitive outcome with the greatest clinical relevance is preferred (e.g., iADRS, CDR-SB). Differences in means, hazard ratios, and other estimates are reported as provided in the primary publications. ARIA = amyloid-related imaging abnormalities; CDR-SB = Clinical Dementia Rating Sum of Boxes; iADRS = Integrated Alzheimer's Disease Rating Scale; TEAE = treatment-emergent adverse events. Source: Author, 2025.

outperforming CSF.[48,49] Studies show that subtle executive dysfunction correlates with amyloid PET positivity and hippocampal atrophy, supporting its use in preventive trials.[49] Plasma biomarkers are transitioning from diagnostics to predictors of treatment response and ARIA risk.

Lifestyle/nutritional strategies remain low-risk options. The LipiDiDiet trial (311 prodromal AD patients) showed slowed NTB decline and reduced hippocampal atrophy (Soininen et al., 2021). Meta-analyses confirm modest risk reduction, with smaller effects than pharmacological therapies.[50,51]

In summary, 2020−2025 marked the first regulatory validation of anti-amyloid antibodies. Benefits remain modest (<1 CDR-SB point), risks and costs are high, and trial populations poorly reflect real-world patients. Nonetheless, diversification into microbiota, metabolic, nutritional, and biomarker-driven strategies suggests a shift toward safer, more accessible interventions that may more broadly impact Alzheimer's disease management.

Parkinson's disease and the emergence of potential neuroprotective strategies

In recent years, clinical research in Parkinson's disease has shifted beyond dopaminergic symptomatic therapies toward approaches with neuroprotective and metabolic potential and strategies targeting non-motor symptoms (Table 2).

The Phase II LIXIPARK trial evaluating lixisenatide reported a mean difference of −3.08 points on the MDS-UPDRS III at 12 months versus placebo ($P = 0.007$). Notably, this effect persisted after a two-month washout, supporting the hypothesis of pharmacological neuroprotection.[52] Although unprecedented after decades of negative trials, the study was limited by its modest sample size (∼158 patients), short follow-up, and high incidence of gastrointestinal adverse events (nausea ∼47%; vomiting ∼13%), which may limit adherence and use. A large multicenter Phase III trial is therefore essential to determine whether lixisenatide represents a true breakthrough or another "false positive" in a field marked by previous disappointments.[53]

Parallel programs targeting genetic pathways have also advanced. In GBA1 mutation carriers, the Phase 1B study of LTI-291 (BIA-28-6156) demonstrated dose-proportional pharmacokinetics, CSF penetration (CSF/plasma ≈ 1), and lysosomal pathway engagement, with transient increases in glycosphingolipids in PBMCs. No clinical benefit emerged, but the safety profile was acceptable.[54] Similarly, LRRK2 inhibition with BIIB122 (DNL151) achieved robust target engagement—reductions of up to 98% in pS935-LRRK2, 93% in pRab10, and 74% in urinary BMPs—in both healthy volunteers and patients, without serious adverse events.[55] These findings provide strong proof of mechanism but await clinical translation.

Advances in structural biology and preclinical models have refined the understanding of pathogenesis. Biophysical assays show that α-synuclein fibrils exhibit conformational heterogeneity that influences toxicity.[56] Targeting this mechanism, peptide inhibitors blocking the α-synuclein −ESCRT interaction reduced dopaminergic degeneration in preclinical models, supporting strategies aimed at reducing pathological aggregates while restoring physiological

Table 2 Pivotal trials in Parkinson's disease (2020−2025): motor effects and safety.

NCT	Intervention	Fase	n	Endpoint primário	Main result	Security
NCT03439943	Lixisenatide (GLP-1 RA) vs. placebo	II	156	MDS-UPDRS III (12m, ON)	Δ = −3.08 points (95% KI 0.86-5,30; $P = 0.007$)	Nausea 46%, vomiting 13%
NCT04760769	Tavapadon (D1/D5 partial agonist)	III (Open)	992	UPDRS Part III / Engine OFF	Pending results	Headache, nausea; profile under study
NCT05357989	Buntanetap (posiphen, anti-amiloidogênico) vs placebo	III	523	MDS-UPDRS (12m)	In progress	Good preliminary tolerability
NCT05778617	Ambroxol (lysosomal modulator, GCase) vs placebo	III	330	Motor/cognitive progression	Expected results	Mild GI effects; favorable profile
NCT04226248	Transdermal rivastigmine vs placebo (CHIEF-PD)	III	600	Reduction of falls	Pending results	Known security profile
NCT06068465	Pimavanserin (PD psychosis) vs placebo	III	248	Reduction of psychotic symptoms	Pending results	Hallucinations, QTc prolongation monitored

Synthesis of trials with the greatest disease-modifying potential and key studies in non-motor symptoms. Columns include: NCT, intervention/class, phase, n, primary endpoint (e.g., MDS-UPDRS III; ON/OFF status and time), primary outcome (metric, effect, 95% CI, p when available), and safety (GI, psychiatric, cardiovascular events, etc.). Notes: For trials with washout, the post-washout outcome is described when applicable. Phase II results are presented as a clinical signal and require confirmation. GI = gastrointestinal; MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale. Source: Author, 2025.

function.[57] Recent structural studies further reveal that distinct α-synuclein conformations differentially regulate synaptic seeding efficiency, suggesting that conformation-specific therapies may outperform nonspecific approaches.[58]

In the translational arena, hybrid approaches integrating biotechnology and neurotechnology are emerging. AI-based platforms combined with optogenetics have produced functional recovery in murine models, advancing the concept of systems for diagnosis, real-time monitoring, and intervention.[59] Cell-based strategies have also progressed: transplantation of dopaminergic progenitors derived from induced pluripotent stem cells has shown safety and early evidence of integration in Phase I/II trials.[60] For diagnostics, PET-FDG combined with SWI imaging has improved differentiation between Parkinson's disease and atypical parkinsonian syndromes, reinforcing the value of multimodal imaging.[61]

Non-pharmacological interventions remain relevant though heterogeneous. A randomized trial of home-based exergames showed no superiority over active controls in gait outcomes (ΔSWST −3.71 s vs −0.71 s; $P = 0.61$), indicating that not all digital innovations yield meaningful benefit.[62] Conversely, a meta-analysis of biofluid microRNAs confirmed their diagnostic and progression utility (sensitivity 0.82; specificity 0.80; AUC 0.87; serum AUC 0.89), supporting multimarker panels for early stratification.[63] Complementary genomic studies expanded the repertoire of risk loci—prioritizing SNCA, LRRK2, GBA1, RIT2, BAG3, and TMEM175—reinforcing opportunities for personalized medicine.[64]

Despite this expansion, methodological critiques persist. Recent recommendations emphasize defining clinically meaningful progression as ≥5 points on the MDS-UPDRS III in the OFF state and adopting time-to-event analyses to reduce symptomatic confounding.[65] Comparative reviews note that, while emerging therapies show promise, absolute clinical gains remain modest and often lack generalizability without large-scale validation.[66,67]

In summary, Parkinson's disease research from 2020 to 2025 is marked by substantial clinical and mechanistic advances: lixisenatide has produced the first consistent signal of neuroprotection (−3.08 points on MDS-UPDRS III; $P = 0.007$), GBA1- and LRRK2-targeted programs have achieved solid proof of mechanism, molecular and digital biomarkers are gaining validation, and cell therapies and hybrid neurotechnologies are progressing toward clinical application. Nonetheless, the field remains vulnerable to repeating cycles of "false positives." Only long-term, multicenter, biomarker-guided Phase III trials will determine whether these advances translate into unequivocal therapeutic benefits with real-world impact.

Multiple sclerosis between the consolidation of established therapies and the uncertainty of new classes

Clinical research in multiple sclerosis between 2020 and 2025 advanced along two main axes: new disease-modifying therapies (DMTs), notably Bruton's tyrosine kinase (BTK) inhibitors, and refinement of established strategies such as anti-CD20 antibodies and cladribine (Table 3).

The largest trials, evolutionRMS1/2 (NCT04338022; NCT04338061), evaluated the BTK inhibitor evobrutinib in more than 2,200 patients with relapsing-remitting multiple

Table 3 Pivotal trials in multiple sclerosis (2020–2025): disease activity, progression, and safety.

NCT	Intervention	Phase	n	Endpoint primário	Main result	Security
NCT04338022 / NCT04338061	Evobrutinibe (BTK inibidor) vs teriflunomida	III	2.290	ARR (156s)	Non-superior: RR 1.02 and 1.00 vs teriflunomide (P>0.5)	ALT ≥5 × ULN in 5% (vs <1%); 3 Hy's law cases; 2 unrelated deaths
NCT06675955	Ocrelizumab (anti-CD20, extension)	III	500	Prolonged physical function	Data still being collected	Known safety profile, risk of infection
NCT05999604	Ocrelizumab (annual vs. semiannual doses)	III	244	Absence of Radiological Activity (NEDA)	Pending results	Security under evaluation
NCT05296161	Ocrelizumabe (B-cell tailored)	IV	296	Adapted dose strategy	Results in progress	Expected reduction in AEs related to immunosuppression
NCT04776213	Mavenclad® (cladribine, extension)	IV	280	Cognition and HRQoL after 3–4 years	Results in progress	Profile consistent with previous use
NCT04057898	MN-166 (ibudilast) vs placebo	II/III	230	ALS progression (off-label)	Mixed study; heterogeneous preliminary results	Nausea, fatigue; reasonable tolerability

Comparative table of the main multiple sclerosis trials during the period, focusing on ARR, radiological activity, and dose optimization strategies (anti-CD20) and new classes (BTK). Columns include: NCT, intervention/class, phase, n, primary endpoint (e.g., ARR, NEDA), main outcome (metric, effect, 95% CI, p when available), and safety (hepatotoxicity, infections, serious events). Notes: Negative trials are explicitly indicated; ongoing studies are marked as "pending." ARR = annualized relapse rate; BTK = Bruton's tyrosine kinase; NEDA = no evidence of disease activity. Source: Author, 2025.

sclerosis. The drug showed no superiority in annualized relapse rate (ARR) compared with teriflunomide (RR 1.02 and 1.00; $P>0.5$). Significant liver enzyme elevations occurred, including three Hy's law cases that resolved after discontinuation.[68] These findings dampened expectations and suggested BTK inhibitors may be more relevant for progressive multiple sclerosis, where innate immunity is dominant.[69]

Anti-CD20 antibodies consolidated their status as therapeutic mainstays. Ocrelizumab sustained 70-80% ARR reductions versus interferon beta and achieved no evidence of disease activity (NEDA) in ~48% of patients after three years.[70] Studies have examined individualized dosing based on B-cell reconstitution to reduce infection risk. Cladribine (Mavenclad®) strengthened its role as an induction therapy: in long-term extensions, 45-50% of patients remained relapse-free for up to four years, with a 58% ARR reduction versus placebo and a stable safety profile.[50] Progress during this period has been incremental, driven by refinement rather than disruptive innovation.[66]

Environmental and metabolic factors gained prominence. A meta-analysis showed low serum vitamin D was associated with a 50-60% increased relapse risk, whereas supplementation reduced fatigue by 6-8 Fatigue Severity Scale points and correlated with lower progression.[71,72] Microbiome studies identified ~35% lower MUC2 expression and a 40% increase in mucin-degrading bacteria, linking dysbiosis to disease acceleration.[73]

Non-pharmacological interventions also showed measurable effects. A randomized trial of high-intensity resistance training produced a 20-25% increase in VO_2 max and a 0.5-0.7-point EDSS reduction within 16 weeks, similar to short-term effects of some DMTs.[74]

In personalized medicine, genetic and epigenetic biomarkers emerged as predictors. The HLA-A*03:01 allele doubled the likelihood of response to glatiramer acetate (55-60% vs. 25-30%).[75] Meta-analyses of microRNAs reported diagnostic accuracy with AUC 0.78-0.85, indicating potential for therapeutic stratification[76].

Disease heterogeneity received increased attention. Around 5% of cases are late-onset, associated with faster progression and a nearly 30% shorter time to reach EDSS 6.0 compared with young-onset multiple sclerosis.[69] In pediatric multiple sclerosis, gaps in long-term safety evidence persist.[77] The pivotal ublituximab trial versus teriflunomide reported an ARR of 0.07 versus 0.19 (62% reduction), with 96% free of new MRI lesions at 96 weeks, though with more respiratory infections (48% vs. 37%).[78]

Overall, the 2020-2025 landscape underscores the consolidation of anti-CD20 antibodies and cladribine as therapeutic pillars, while BTK inhibitors fell short in relapsing disease. Evidence from vitamin D, microbiome studies, pharmacogenomic biomarkers, and physical training suggests future progress will rely on integrated approaches bridging pharmacology, personalized medicine, and lifestyle strategies. Innovation in multiple sclerosis is unlikely to arise from a single agent but from complementary approaches.

Across major neurodegenerative diseases, distinct patterns emerge: regulatory approval of anti-amyloid agents in Alzheimer's disease, initial signals of neuroprotection in Parkinson's disease, and incremental consolidation in multiple sclerosis. Fig. 1 summarizes the principal therapeutic mechanisms investigated.

Cross-sectional comparison between Alzheimer's, Parkinson's and multiple sclerosis

A comparative analysis of clinical trials conducted between 2020 and 2025 across Alzheimer's disease,

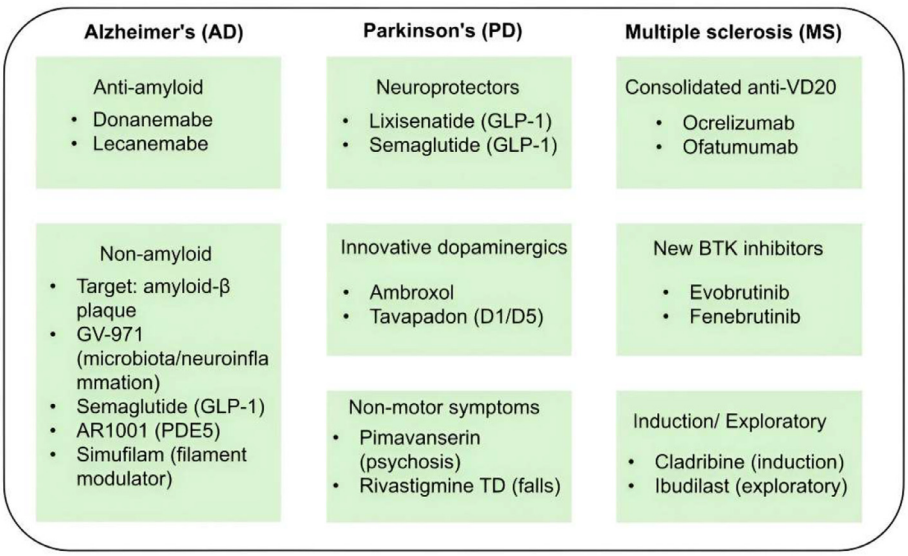

Fig. 1 Therapeutic mechanisms investigated in Alzheimer's, Parkinson's, and multiple sclerosis (2020-2025).

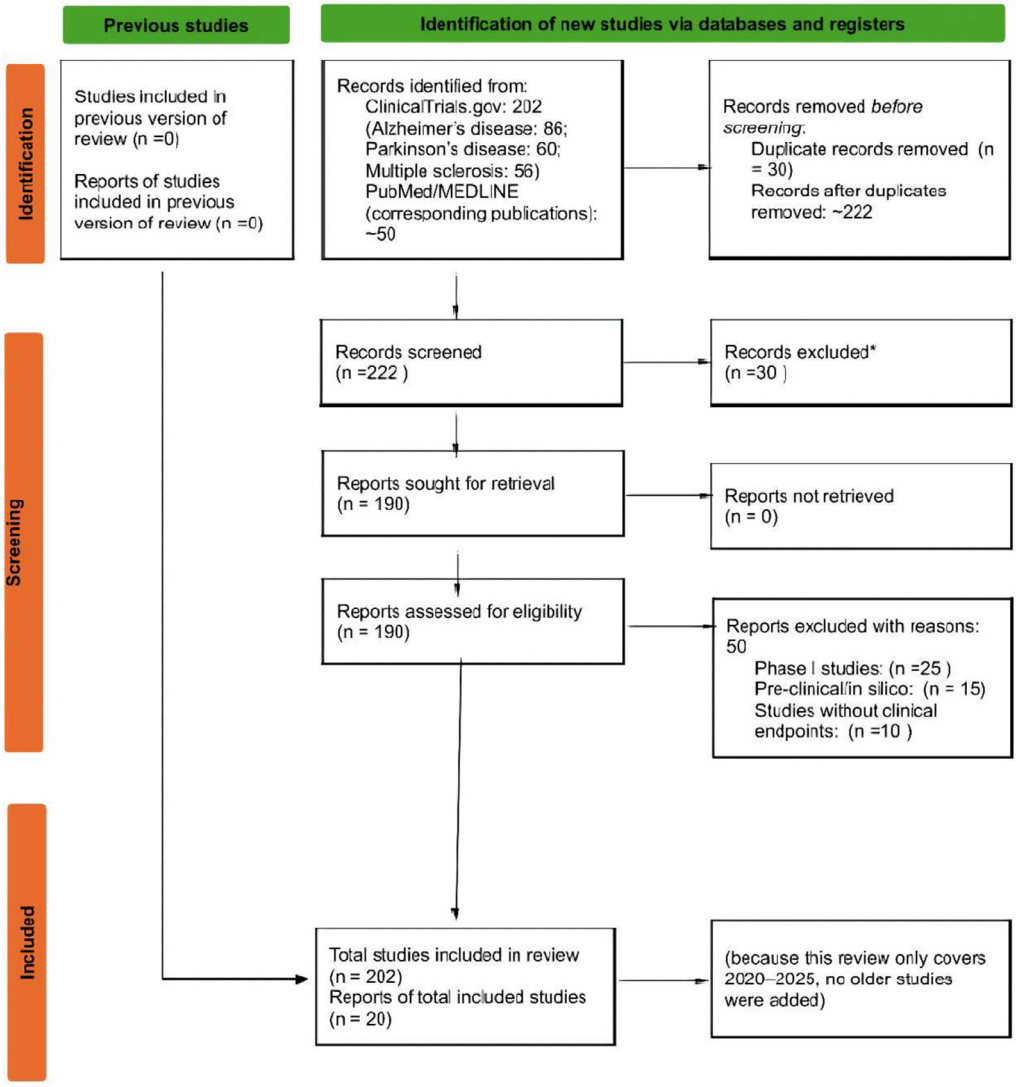

Fig. 2 PRISMA 2020 flow diagram of study selection.
*(e.g., observational, diagnostic-only, or not interventional). The diagram summarizes the identification, screening, eligibility, and inclusion of interventional clinical trials between January 2020 and December 2025. Records were identified from ClinicalTrials.gov (n = 202) and PubMed/MEDLINE (≈50 corresponding reports). After removal of duplicates and exclusion of Phase I, pre-clinical, or observational studies, 202 Phase II–IV clinical trials were included in the final synthesis. Reports of included studies correspond to ~20 peer-reviewed publications. No previous version of this review existed; therefore, the boxes "Studies included in previous version" and "Reports of studies included in previous version" were filled with (n = 0). Source: adapted from Page MJ et al., *BMJ* 2021;372:n71.

Parkinson's disease, and multiple sclerosis reveals marked differences in therapeutic impact and implementation challenges Fig. 2.[40]

In Alzheimer's disease, anti-amyloid antibodies produced reductions of <1 point on the CDR-SB at 18 months, a statistically significant but clinically modest effect.[17]

In Parkinson's disease, lixisenatide generated a −3.08-point change on the MDS-UPDRS III at 12 months (P = 0.007), suggesting possible neuroprotection, though results remain limited by sample size and lack of Phase III confirmation.[53]

In multiple sclerosis, established therapies such as ocrelizumab sustained 70-80% ARR reductions and NEDA rates near 50%, indicating durable efficacy.[50]

Safety profiles also differ. Alzheimer's disease treatments are limited by ARIA risk, affecting up to 24% of donanemab users, including symptomatic and fatal cases.[41,79] Parkinson's disease GLP-1 agonists frequently caused gastrointestinal adverse events (nausea ~50%, vomiting 13%).[53] In multiple sclerosis, BTK inhibitors failed due to insufficient efficacy and hepatotoxicity, while anti-CD20 therapies carry cumulative infection risks.[68]

Implementation barriers extend beyond efficacy. Alzheimer's disease requires biomarker-based selection (PET, plasma p-tau) and serial MRI, restricting use to specialized centers and increasing costs.[80] GLP-1 agonists in Parkinson's disease remain expensive and largely off-label.[81] Multiple sclerosis therapies such as anti-CD20 agents and cladribine require infusion infrastructure and laboratory monitoring, limiting access in low- and middle-income regions.[71]

Global disparities persist: high-income regions can support anti-amyloid therapy costs, imaging, and individualized anti-CD20 regimens, whereas countries in Latin America, Africa, and Asia face financial and infrastructural barriers, limiting access to these advances.[15,37]

Overall, differences in efficacy, toxicity, and feasibility underscore that regulatory approval alone is insufficient. Progress requires clinically meaningful endpoints, predictive biomarkers, and equitable access policies to translate advances into real-world benefits and reduce global neurological health disparities.[27,38]

Limitations of the evidence

The interpretation of the clinical trials evaluated here requires caution due to several methodological and contextual limitations. First, there is substantial heterogeneity in primary outcomes—iADRS and CDR-SB in Alzheimer's disease, MDS-UPDRS in Parkinson's disease, and ARR/NEDA in multiple sclerosis—which complicates direct comparisons of effect size across conditions. Second, follow-up durations were generally short (12-24 months), limiting assessment of long-term outcomes and durability of effects.

Another limitation is that many trials remain unpublished in full peer-reviewed form, requiring reliance on registry data (e.g., ClinicalTrials.gov), which often lack methodological detail. The predominance of industry-sponsored studies also raises concerns about selective reporting, especially for secondary endpoints and post hoc analyses.

Restrictive inclusion criteria further limit generalizability. In Alzheimer's disease, several trials enrolled only patients with low to intermediate tau levels, not reflecting real-world heterogeneity. In multiple sclerosis, the exclusion of older or comorbid patients likewise reduces applicability to broader clinical populations.

Although this narrative review enables examination of conceptual and methodological issues, the comparative synthesis highlights a persistent gap between reported trial outcomes and independent critical assessments. Table 4 summarizes these advances, limitations, and clinical

Table 4 Recent clinical trials and literature perspectives on neurological diseases.

Illness	Clinical trial findings	Evidence from the literature	Critical interpretation
Alzheimer	Donanemab and lecanemab demonstrated slowing of cognitive decline on scales such as iADRS and CDR-SB (∼25−35%), confirming the amyloid hypothesis; GV-971 showed modest benefit on ADAS-Cog; trials with anti-tau and metabolic modulators still inconclusive.	Modest absolute benefit (<1 point in CDR-SB at 18 months); high incidence of ARIA (up to 24% with donanemab); restrictive inclusion criteria (low/intermediate tau); short follow-up; lack of data in diverse populations.	Clinical use restricted to specialized centers, with biomarkers and serial MRI; need for predictive biomarkers of response and greater long-term safety; alternative non-amyloid therapies still exploratory.
Parkinson	Lixisenatide reduced motor progression by ∼3 points in MDS-UPDRS III at 12 months (P=0.007), effect maintained after washout; tavapadon, ambroxol and buntanetap under investigation; cell therapies (iPS) demonstrated safety in the initial phase; studies also on non-motor symptoms (rivastigmine, pimavanserin).	Small sample sizes (LIXIPARK n≈150); high rate of gastrointestinal events (nausea in ∼50%, vomiting in ∼13%); lack of validated biomarkers of progression; limited follow-up; risk of historical "false positives."	Strongest evidence to date for GLP-1 as a possible neuroprotectant, but not yet replicated in Phase III; promising but immature cellular and metabolic interventions; increasing focus on quality of life and non-motor symptoms.
Multiple sclerosis	Anti-CD20 (ocrelizumab, ublituximab) reduced ARR by 62−80% and achieved NEDA in ∼48% after 3 years; cladribine showed ∼45−50% of patients free of relapse at 4 years; evobrutinib failed in evolutionRMS1/2 (>2,200 patients, RR 1.0 vs teriflunomide); vitamin D reduced fatigue by 6-8 points; resistance training reduced EDSS by 0.5-0.7 points.	BTK inhibitors ineffective in relapsing MS; relevant hepatotoxicity (3 cases of Hy's law with evobrutinib); exclusion of elderly patients and comorbidities; ∼5% of late-onset multiple sclerosis underrepresented; short follow-up in non-pharmacological interventions.	Anti-CD20 and cladribine remain mainstays; incremental innovation with personalized regimens; BTKs repositioned for progressive multiple sclerosis; environmental and lifestyle factors gain importance; biomarkers (HLA-A*03:01, miRNAs) indicate the future of personalized medicine.

The table summarizes the main clinical findings in Alzheimer's, Parkinson's, and Multiple Sclerosis, comparing results from pivotal studies with reviews, meta-analyses, and mechanistic advances. This synthesis highlights both the potential for regulatory transformation and the limitations of efficacy, safety, and applicability, offering a cross-sectional view of the field. Source: Author, 2025.

implications across Alzheimer's disease, Parkinson's disease, and multiple sclerosis.

Conclusion

The period from 2020 to 2025 marks the clear emergence of course-modifying therapies in neurological diseases. For the first time, interventions have altered clinical trajectories in conditions long considered intractable, creating a new regulatory and scientific landscape. However, these advances remain uneven, modest in absolute effect, and often accompanied by significant risks, underscoring both progress and persistent limitations. The main challenge for the next decade is to convert statistically significant results into meaningful, durable, and equitable clinical benefits. This will require: 1) sensitive predictive biomarkers and functional endpoints that capture real patient impact; 2) integration of pharmacological, environmental, and non-pharmacological strategies into multimodal care; and 3) removal of barriers to access and affordability so that innovations reach patients outside specialized centers. The goal is not simply to mark regulatory achievements but to establish a practical paradigm shift that links biomedical innovation with implementation. Only then will disease-course modification move beyond statistical improvement and become a transformative reality for patients worldwide.

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Declaration of competing interest

The authors declare that they have no conflicts of interest related to the preparation and publication of this work: Pedro César de Souza; Thaynara Paula Warren Bezerra; Moacyr Jesus Barreto de Melo Rêgo; Michelle Melgarejo da Rosa.

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