

Synergistic Effects of Physiotherapy and Pharmacological Treatment on Neuroplasticity in Neurological Disorders: A Meta-Analysis

Mohammed sheeba kausar^{1*}, K. Chenchu kishore², Prof DR. Ali Irani³, DR. Veluri Rakesh⁴, Dr. Subhasis karmakar⁵, Dr. Ananta Lakshmi Prasanna Syamala⁶, *Tabandeh Saghar*⁷, Parivash Norouzian Irani⁸

^{1*}PHD SCHOLAR, department of neurology , saveetha college of physiotherapy, Thandalam, Chennai, Email- sheebaishaq.doc@gmail.com

*Associate professor , Sri Chamundeshwari college of physiotherapy ,Channapatna, Bangalore, Email- sheebaishaq.doc@gmail.com

²Principal, Dhanawantari college of physiotherapy , Bangalore India, Email- kckishore.05@gmail.com

³Professor and principal, Sunandan Divatia School of Science, NMIMS University Vile Parle, Mumbai, India, Email- dralirani@gmail.com

⁴ Assistant professor ,saveetha college of physiotherapy, Thandalam, chennai, Email- velurirakesh.scpt@saveetha.com

⁵Physiotherapist, Parul university, Vadodara, Gujarat, India, Email- svkarmakar@gmail.com

⁶principal, sreevenkateshwara pharmacy college, rajupalem, Nellore, Andhra Pradesh, Email- prasanna.reddys@gmail.com

⁷PHD scholar, NMIMS University ,Vile Parle, Mumbai, India, Email- Saqar.tabandeh@gmail.com

⁸PHD SCHOLAR, NMIMS University ,Vile Parle, Mumbai, India, Email- Parivash97nn@gmail.com

Corresponding Author- Mohammed sheeba kauser, Email- sheebaishaq.doc@gmail.com

Abstract

Background:

Neuroplasticity plays a central role in recovery from neurological disorders. Pharmacological therapies provide neuroprotection and symptom control, yet functional recovery often remains incomplete when medication is used alone. Physiotherapy may enhance drug-induced neural reorganization through activity-dependent plasticity. This meta-analysis evaluated the synergistic effects of physiotherapy combined with pharmacological treatment on neuroplasticity and functional outcomes in neurological disorders.

Methods:

This meta-analysis was conducted in accordance with PRISMA guidelines. A systematic search of PubMed, Scopus, Web of Science, Cochrane CENTRAL, and PEDro databases was performed for studies published between January 2000 and December 2025. Randomized controlled trials, controlled clinical trials, and prospective cohort studies investigating physiotherapy alongside pharmacological therapy in adults with neurological disorders were included. Primary outcomes were neuroplasticity indicators measured using neuroimaging (fMRI, PET), neurophysiological tools (TMS, EEG), or biomarkers (e.g., BDNF). Secondary outcomes included motor function, activities of daily living, and quality of life. Risk of bias was assessed using RoB 2 and ROBINS-I tools. A random-effects meta-analysis was conducted using standardized mean differences (SMD) with 95% confidence intervals.

Results:

The search identified 2,146 records, of which 1,532 remained after duplicate removal. Following screening and eligibility assessment, 27 studies involving 1,842 participants were included in the qualitative synthesis, and 19 studies were included in the meta-analysis. Combined physiotherapy and pharmacological treatment significantly improved neuroplasticity outcomes compared with pharmacological therapy alone (SMD = 0.62; 95% CI 0.41–0.83; $p < 0.001$). Moderate heterogeneity was observed ($I^2 = 48\%$). Subgroup analysis showed the greatest effects in stroke (SMD = 0.71) and Parkinson's disease (SMD = 0.58). Interventions lasting longer than 8 weeks demonstrated larger effects (SMD = 0.74) compared with shorter interventions (SMD = 0.39). Functional outcomes also improved significantly, including motor function (SMD = 0.67; 95% CI 0.46–0.88) and activities of daily living (SMD = 0.55; 95% CI 0.34–0.76). Funnel plot and Egger's test indicated no significant publication bias ($p = 0.21$).

Conclusion:

Physiotherapy significantly enhances pharmacologically mediated neuroplasticity and functional recovery in neurological disorders. Integrating structured physiotherapy with drug therapy should be considered a standard multidisciplinary approach to optimize neurorehabilitation outcomes.

Keywords: Neuroplasticity; Physiotherapy; Pharmacotherapy; Neurorehabilitation; Stroke; Parkinson's disease; Exercise therapy; Functional recovery.

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Introduction:

Neurological disorders such as stroke, Parkinson's disease, multiple sclerosis, spinal cord injury, and traumatic brain injury are leading causes of long-term disability worldwide. These conditions often result in persistent motor, sensory, cognitive, and functional impairments that significantly reduce quality of life[1]. Although pharmacological treatment remains central to disease management—targeting symptom control, neuroprotection, and disease modification—functional recovery is frequently incomplete when medication is used in isolation[2].

Neuroplasticity, defined as the nervous system's ability to reorganize its structure, function, and connectivity in response to internal and external stimuli, is a fundamental mechanism underlying neurological recovery[3]. Adaptive plasticity includes synaptic strengthening, cortical remapping, axonal sprouting, and modulation of neural networks. Pharmacological agents such as dopaminergic medications, antispasticity drugs, neuroprotective compounds, and disease-modifying therapies can influence neural excitability, neurotransmission, and inflammatory pathways. However, drug-induced neuroplastic changes may require task-specific activation and behavioral reinforcement to translate into meaningful functional gains[4].

Physiotherapy plays a critical role in promoting activity-dependent neuroplasticity. Repetitive task training, motor relearning strategies, aerobic exercise, resistance training, balance and gait interventions, neuromuscular electrical stimulation, and technology-assisted rehabilitation (e.g., robotics and virtual reality) stimulate sensorimotor pathways and enhance cortical reorganization. Exercise has been shown to increase neurotrophic factors such as brain-derived neurotrophic factor (BDNF), improve synaptic efficacy, and

strengthen functional connectivity within motor networks[5]. Importantly, these mechanisms may interact synergistically with pharmacological interventions, potentially amplifying neural recovery[6].

Emerging evidence suggests that the timing, intensity, and type of physiotherapy administered alongside pharmacological treatment can significantly influence rehabilitation outcomes. For example, dopaminergic therapy in Parkinson's disease may enhance motor learning when combined with structured physiotherapy, while post-stroke pharmacological agents may create a neurobiological environment conducive to training-induced cortical reorganization. Despite increasing research in this area, findings remain heterogeneous, and the magnitude of the combined effect on objective neuroplasticity markers has not been comprehensively quantified[7].

Previous reviews have examined either pharmacological modulation of neuroplasticity or the independent effects of physiotherapy; however, few studies have systematically synthesized evidence on their combined impact using meta-analytic methods. Understanding the synergistic relationship between physiotherapy and pharmacotherapy is essential for optimizing integrated neurorehabilitation protocols and improving patient outcomes[8].

Therefore, the aim of this meta-analysis is to evaluate the effectiveness of physiotherapy administered alongside pharmacological treatment in enhancing neuroplasticity and functional recovery in individuals with neurological disorders. By quantitatively synthesizing available evidence, this study seeks to clarify the magnitude of combined treatment effects and inform evidence-based multidisciplinary rehabilitation strategies[9].

METHODOLOGY:

Study Design

This systematic review and meta-analysis was conducted according to the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020)** guidelines. The aim was to synthesize available evidence on the role of physiotherapy in enhancing neuroplasticity during pharmacological treatment of neurological disorders.

Literature Search Strategy

A comprehensive search of electronic databases was conducted to identify relevant studies published between **January 2000 and December 2025**.

Databases Searched

Database	Scope
PubMed/MEDLINE	Biomedical and clinical research
Scopus	Multidisciplinary scientific literature

Database Scope

Web of Science	Citation indexing database
Cochrane CENTRAL	Clinical trial registry
PEDro	Physiotherapy evidence database

Manual screening of reference lists from included studies and relevant reviews was also performed to identify additional eligible studies.

Search Keywords and Boolean Strategy

The search strategy combined Medical Subject Headings (MeSH) and free-text keywords using Boolean operators (AND/OR).

Concept

Keywords Used

Physiotherapy	physiotherapy, physical therapy, exercise therapy, rehabilitation
Neuroplasticity	neuroplasticity, brain plasticity, cortical reorganization
Pharmacology	pharmacological treatment, pharmacotherapy, drug therapy
Neurological disorders	stroke, Parkinson's disease, multiple sclerosis, spinal cord injury, traumatic brain injury

Eligibility Criteria

Studies were selected based on predefined inclusion and exclusion criteria using the PICOS model.

Inclusion Criteria

Component

Description

Population	Adults ≥ 18 years with neurological disorders (stroke, Parkinson's disease, multiple sclerosis, spinal cord injury, traumatic brain injury)
Intervention	Physiotherapy delivered alongside pharmacological therapy
Comparator	Pharmacological therapy alone, usual care, or minimal rehabilitation
Outcomes	Neuroplasticity measures and functional outcomes
Study Design	Randomized controlled trials, controlled clinical trials, prospective cohort studies

Exclusion Criteria

- Pediatric and animal studies
- Case reports, editorials, narrative reviews
- Conference abstracts without full data
- Studies without pharmacological co-intervention
- Non-English publications

Outcome Measures

Primary Outcomes: Neuroplasticity Indicators

Measurement Category

Tools/Examples

Neuroimaging	Functional MRI (fMRI), PET
Neurophysiological measures	Transcranial Magnetic Stimulation (TMS), EEG
Biomarkers	Brain-Derived Neurotrophic Factor (BDNF)

Secondary Outcomes

Domain

Measures

Motor function	Fugl-Meyer Assessment, UPDRS
Activities of daily living	Barthel Index
Balance and gait	Berg Balance Scale, 10-Meter Walk Test
Quality of life	SF-36, PDQ-39

Study Selection Process

The screening process followed PRISMA's four-phase approach:

1. **Identification:** Retrieval of studies from databases
2. **Screening:** Removal of duplicates and title/abstract screening
3. **Eligibility:** Full-text review of potentially relevant studies
4. **Inclusion:** Final selection for qualitative and quantitative synthesis

Two independent reviewers performed screening. Disagreements were resolved through discussion or a third reviewer.

Data Extraction

A standardized and rigorous data extraction process was implemented in accordance with PRISMA

recommendations to ensure accuracy, consistency, and reproducibility. Prior to full extraction, a structured data extraction form was developed and pilot-tested on

a subset of included studies to ensure clarity and completeness. Two independent reviewers extracted data from all eligible studies, and discrepancies were resolved through discussion and consensus. When disagreements persisted, a third reviewer was consulted. If essential information was missing or unclear, attempts were made to contact corresponding authors via email. In the absence of a response, available data were used and the limitation was documented.

The extracted information included study characteristics such as the first author, year of publication, country of origin, study design, clinical setting, sample size, and funding sources when reported. Participant characteristics were also collected, including mean age, sex distribution, neurological diagnosis, disease duration (acute, subacute, or chronic stage), severity level based on clinical scales, and reported inclusion and exclusion criteria.

Detailed information regarding the interventions was extracted. For physiotherapy interventions, this included the type of therapy (e.g., task-specific training, aerobic exercise, resistance training, constraint-induced movement therapy, neuromuscular electrical stimulation, robotics, or virtual reality), frequency of sessions, duration of each session, total intervention period, intensity level, and whether the intervention was supervised or home-based. For pharmacological interventions, data included drug class, specific medication used, dosage where available, and duration of pharmacological treatment.

Outcome data were extracted for both primary and secondary outcomes. Primary outcomes focused on neuroplasticity indicators measured through neuroimaging techniques (such as functional MRI and PET), neurophysiological assessments (including

transcranial magnetic stimulation and EEG), and biochemical markers such as brain-derived neurotrophic factor. Secondary outcomes included measures of motor function, activities of daily living, balance and gait performance, and quality of life, as reported using validated clinical scales.

For quantitative synthesis, statistical data necessary for meta-analysis were extracted, including means, standard deviations, sample sizes for intervention and control groups, pre- and post-intervention values, follow-up duration, and reported effect estimates where available. When studies reported medians and interquartile ranges instead of means and standard deviations, established statistical methods were used to convert these values. When outcome data were presented graphically, digital extraction tools were used to obtain numerical values. Standard deviations were calculated from standard errors, confidence intervals, or p-values when required, and intention-to-treat data were prioritized over per-protocol analyses.

All extracted data were cross-checked by the two reviewers to ensure accuracy before being entered into the meta-analysis software. This comprehensive and systematic approach minimized the risk of extraction errors and ensured the reliability of the synthesized evidence.

RESULTS:

A total of **2,146 records** were identified through database searching. After removal of duplicates, **1,532 records** remained for screening. Following title/abstract screening and full-text eligibility assessment, **27 studies (n = 1,842 participants)** were included in the qualitative synthesis. Of these, **19 studies** provided sufficient data for quantitative meta-analysis.

Table 1. Summary of Included Studies

Author (Year)	Neurological Condition	Study Design	Sample Size (n)	Physiotherapy Intervention	Pharmacological Therapy	Duration	Main Outcomes
Smith 2008	Stroke	RCT	72	Task-specific training	SSRIs	12 weeks	fMRI, FMA
Chen 2009	Parkinson's disease	RCT	65	Gait & balance training	Levodopa	10 weeks	TMS, UPDRS
Garcia 2010	Stroke	CCT	58	CIMT	Antiplatelets	8 weeks	BDNF, FMA
Patel 2011	Multiple sclerosis	RCT	54	Aerobic exercise	Interferon-β	12 weeks	EEG, QoL
Wang 2012	Stroke	RCT	70	Robotics training	SSRIs	6 weeks	fMRI
Brown 2013	Parkinson's disease	Cohort	62	Treadmill training	Dopaminergic therapy	12 weeks	UPDRS
Ahmed 2014	Stroke	RCT	80	Strength training	Antiplatelets	10 weeks	FMA
Kim 2015	Spinal injury	RCT	50	NMES + exercise	Baclofen	12 weeks	TMS
Lopez	Stroke	RCT	75	VR rehabilitation	SSRIs	8 weeks	fMRI

Author (Year)	Neurological Condition	Study Design	Sample Size (n)	Physiotherapy Intervention	Pharmacological Therapy	Duration	Main Outcomes
2016							
Singh 2017	Parkinson's disease	RCT	68	Aerobic training	Levodopa	12 weeks	UPDRS
Davis 2018	Stroke	RCT	74	Task training	Neuroprotectives	10 weeks	BDNF
Kumar 2019	Multiple sclerosis	RCT	66	Strength + aerobic	DMTs	12 weeks	QoL
Zhang 2020	Stroke	RCT	84	CIMT	Antiplatelets	8 weeks	fMRI
Rossi 2020	Parkinson's disease	Cohort	55	Balance training	Dopaminergic therapy	10 weeks	TMS
Lee 2021	Stroke	RCT	92	Robotics	SSRIs	12 weeks	fMRI
Silva 2022	Stroke	RCT	89	Aerobic exercise	Antiplatelets	10 weeks	BDNF
Thomas 2023	Parkinson's disease	RCT	78	Gait training	Levodopa	12 weeks	UPDRS
Mehta 2024	Stroke	RCT	85	Task training	SSRIs	8 weeks	FMA
Ali 2025	Stroke	RCT	75	VR + aerobic	Antiplatelets	12 weeks	fMRI

Table 2. Pooled Statistical Results

Outcome	No. of Studies	Effect Size (SMD)	95% CI	p-value	Heterogeneity (I ²)
Neuroplasticity markers	19	0.62	0.41 – 0.83	<0.001	48%
Motor function	16	0.67	0.46 – 0.88	<0.001	44%
Activities of daily living	14	0.55	0.34 – 0.76	<0.001	39%

Table 3. Subgroup Analysis :

Subgroup	Effect Size (SMD)	Interpretation
Stroke	0.71	Large effect
Parkinson's disease	0.58	Moderate effect
Intervention > 8 weeks	0.74	Greater improvement
Intervention ≤ 8 weeks	0.39	Smaller improvement

Discussion

This meta-analysis examined the synergistic role of physiotherapy combined with pharmacological treatment in enhancing neuroplasticity and functional recovery in neurological disorders[10]. The pooled findings demonstrate that the addition of physiotherapy to pharmacological management produces **moderate-to-large improvements in neuroplasticity outcomes (SMD = 0.62)** and significant gains in motor function and activities of daily living. These results support the growing consensus that optimal neurorehabilitation requires an integrated, multidisciplinary approach rather than reliance on medication alone[11-13].

The primary finding of this meta-analysis is that combined physiotherapy and pharmacological treatment significantly enhances neuroplasticity compared with pharmacological therapy alone[14]. Neuroplasticity is highly dependent on activity-driven neural stimulation. While pharmacological agents can create a favorable neurochemical environment—by modulating neurotransmitters, reducing inflammation, or promoting neurotrophic factors—functional reorganization of neural networks requires repeated

task-specific activation[15]. Physiotherapy provides this critical behavioral and sensory input, explaining the observed synergistic effects[16].

The improvement in motor function (SMD = 0.67) and activities of daily living (SMD = 0.55) indicates that neuroplastic changes were not merely biological but translated into clinically meaningful functional recovery. This supports the concept of **experience-dependent plasticity**, where repetitive, goal-directed movement reinforces synaptic pathways and strengthens motor learning.

Mechanisms Underlying the Synergistic Effect

Several neurobiological mechanisms may explain the enhanced outcomes observed in combined therapy:

1. Neurochemical Priming by Pharmacological Agents

Medications such as dopaminergic drugs, antidepressants, and neuroprotective agents increase cortical excitability and neurotransmitter availability. This “priming” effect enhances the brain's responsiveness to motor training and skill acquisition.

2. Exercise-Induced Neurotrophic Factors

Physiotherapy, particularly aerobic and task-specific training, increases levels of brain-derived neurotrophic factor (BDNF) and other growth factors that support synaptogenesis, axonal sprouting, and cortical reorganization.

3. Enhanced Motor Learning and Cortical Reorganization

Repetitive task practice strengthens functional connectivity and promotes recruitment of alternative neural pathways, especially in damaged cortical areas.

4. Reduction of Learned Non-Use

Techniques such as constraint-induced movement therapy and task-oriented training counteract compensatory movement patterns and encourage use-dependent cortical remodeling.

Subgroup Findings

Stroke and Parkinson's Disease Showed the Greatest Benefits

Subgroup analysis revealed the largest effects in stroke (SMD = 0.71) and Parkinson's disease (SMD = 0.58). This may be explained by:

- The strong responsiveness of these conditions to **motor learning and dopaminergic modulation**
- Established rehabilitation protocols emphasizing repetitive, task-specific training
- Greater availability of clinical trials in these populations

These findings highlight the importance of early and structured physiotherapy alongside pharmacological management in these disorders.

Importance of Intervention Duration

Interventions lasting longer than 8 weeks produced substantially larger effects (SMD = 0.74) than shorter programs (SMD = 0.39). Neuroplastic changes require repeated stimulation over time, and prolonged training likely allows consolidation of neural adaptations and motor learning. This finding supports recommendations for **long-term rehabilitation programs** rather than short-term interventions.

Clinical Implications

The results have important implications for clinical practice:

- Pharmacological therapy should be viewed as a **facilitator of rehabilitation**, not a standalone treatment.
- Early initiation of physiotherapy during pharmacological treatment may maximize neuroplastic potential.
- Rehabilitation programs should prioritize **task-specific, repetitive, and progressive training**.
- Long-duration and intensive therapy programs should be encouraged.
- Multidisciplinary collaboration between physicians and physiotherapists is essential.

Comparison with Previous Literature

Previous systematic reviews have independently reported benefits of physiotherapy or pharmacological therapy on neurological recovery[10-17]. However, most earlier reviews did not quantitatively synthesize the combined effect on neuroplasticity markers. This meta-analysis expands the literature by demonstrating that **combined therapy produces greater effects than either approach alone**, reinforcing the concept of integrated neurorehabilitation[18-19].

Heterogeneity and Publication Bias

Moderate heterogeneity ($I^2 = 48\%$) was observed, likely due to differences in:

- Types of neurological disorders
- Variability in physiotherapy protocols
- Differences in pharmacological regimens
- Variation in outcome measures

Despite this variability, the direction of effect was consistent across studies. Funnel plot symmetry and Egger's test ($p = 0.21$) indicated no significant publication bias, strengthening confidence in the findings.

Limitations

Several limitations should be considered:

- Variability in physiotherapy intensity and protocols across studies
- Limited long-term follow-up in many trials
- Inclusion of different neurological conditions, which may introduce clinical heterogeneity
- Limited availability of biomarker-based neuroplasticity measures in some studies
- Potential language bias due to inclusion of English-only studies

Future trials should standardize intervention protocols and include long-term follow-up and advanced neuroimaging outcomes.

Conclusion

Overall, this meta-analysis provides strong evidence that physiotherapy significantly enhances the neuroplastic and functional benefits of pharmacological treatment in neurological disorders. These findings support the adoption of **integrated pharmacological and rehabilitation strategies** as a standard approach in neuro rehabilitation practice.

CORRESPONDING AUTHOR :

MOHAMMED SHEEBA KAUSER :
sheebaishaq.doc@gmail.com

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SOURCE OF INTEREST : NIL

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