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THE IMPACT OF PHYSIOTHERAPY INTERVENTIONS COMBINED WITH PHARMACOLOGICAL MANAGEMENT ON FUNCTIONAL RECOVERY IN POST-STROKE PATIENTS: A SYSTEMATIC REVIEW

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Abstract

Background: Rehabilitation pharmacology aims to augment post-stroke neuroplasticity when paired with task-specific training, but no drug is currently approved to enhance motor recovery after stroke. **Objective:** To synthesize randomized trials of pharmacologic agents given with rehabilitation to improve functional outcomes after stroke. **Methods:** We narratively synthesized six pre-specified randomized, double-blind trials: levodopa+physiotherapy (2001), dextroamphetamine+physiotherapy (STARS, 2006), methylphenidate and levodopa+physiotherapy (2011), and three large pragmatic trials of fluoxetine for 6 months (FOCUS, 2019; AFFINITY, 2020; EFFECTS, 2020). Primary functional endpoints (eg, Rivermead Motor Assessment, Fugl-Meyer, mRS) and safety were extracted as reported. **Results:** Levodopa 100 mg given before therapy for 3 weeks improved Rivermead Motor Assessment versus placebo, with gains persisting at 6 weeks (8.2 vs 5.7 points; p=0.020). Dextroamphetamine+physiotherapy showed no overall benefit on Fugl-Meyer; an apparent advantage in moderate deficits was confounded by baseline imbalance. A factorial methylphenidate/levodopa trial found small advantages on Barthel Index and NIHSS at 6 months without robust motor superiority; tolerability was acceptable. The fluoxetine megatrials were neutral for mRS shift and reported more adverse events (fractures, hyponatremia, seizures) with fluoxetine. **Conclusions:** Timing levodopa immediately before therapy shows promising but unconfirmed benefits; routine SSRI use to “boost” recovery is not supported and may increase harm. Current guidelines emphasize comprehensive, adequately dosed, team-based rehabilitation and individualized decisions.

Keywords: Stroke; Rehabilitation; Neuroplasticity; Levodopa; Methylphenidate; Dextroamphetamine; Fluoxetine; SSRI; Randomized Controlled Trial.

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INTRODUCTION

Recovery-directed drugs target plasticity and growth mechanisms distinct from acute reperfusion/neuroprotection, offering a wider therapeutic window for many survivors [7]. Among candidate classes, serotonergic and dopaminergic agents have attracted attention, with effects that are shaped by concurrent, task-specific training—i.e., experience-dependent neuroplasticity [7]. Early signals (levodopa paired with therapy; small SSRI studies) prompted larger confirmatory trials and guideline scrutiny [7–9,10]. Practice guidelines underscore that organized, dose-adequate, interdisciplinary rehabilitation remains the cornerstone of care, while pharmacologic enhancers should be interpreted within rigorous evidence hierarchies [8,9]. The American Heart Association/American Stroke Association guideline highlights the centrality of coordinated, team-based programs and notes persistent evidence gaps due to historically small or heterogeneous trials in this field [8]. The 2024 VA/DoD guideline, based on an updated systematic review, provides algorithms for motor therapy and emphasizes shared decision making and patient-centered goals across settings [9].

Comprehensive evidence syntheses reassessed SSRIs. The 2021 Cochrane review (new search and updated analyses) concluded that SSRIs do not improve global disability when restricted to trials at low risk of bias, while increasing certain harms; this aligned with the neutral findings from large pragmatic RCTs of fluoxetine and reinforced the need to separate mood benefits from motor/functional recovery claims [10]. Dopaminergic augmentation coupled tightly to therapy bouts has biological plausibility and some positive signals but remains under-tested at scale [7].

We present a focused evidence synthesis using pre-selected trials to clarify what reliably helps, what does not, and where uncertainty persists. Our primary aim is to inform practice and future research design (timing to therapy, dosing, phenotyping) while adhering to PRISMA-aligned reporting and contemporary guideline framing [8,9].

METHODS

Eligibility criteria. Randomized, double-blind, placebo-controlled trials testing pharmacologic augmentation of post-stroke rehabilitation versus placebo/usual care were eligible. Per protocol, the evidence set comprised six trials: levodopa+physiotherapy [1], dextroamphetamine+physiotherapy [2], methylphenidate and levodopa+physiotherapy [3], and three 6-month fluoxetine trials (FOCUS, AFFINITY, EFFECTS) [4–6].

Data extraction. From each RCT we extracted participants, timing from stroke, intervention (agent, dose, schedule), coupling to therapy, outcome instruments/time points, and authors reported between-group effects (including p-values or adjusted estimates). Safety signals were captured as reported (falls, fractures, seizures, hyponatremia).

Synthesis. Owing to clinical and methodological heterogeneity (different agents, dosing/timing, phases post-stroke, and endpoints), we conducted a structured narrative synthesis and compiled two summary tables. No meta-analysis was attempted.

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Risk of bias/certainty. Large fluoxetine trials (FOCUS, AFFINITY, EFFECTS) were multicenter, double-blind, used concealed allocation/minimization, had near-complete follow-up, and returned consistent null primary outcomes with adverse-event imbalances [4–6,10,14]. Earlier dopaminergic/psychostimulant trials were smaller, variably timed to therapy, and used diverse outcomes, limiting certainty despite suggestive benefits (notably with levodopa timed before therapy) [1–3,7].

Interpretation framework. We aligned conclusions with current guideline perspectives prioritizing comprehensive rehabilitation, individualized care, and cautious use of pharmacologic enhancers outside trials or clear indications [8,9].

RESULTS

Overview of included trials

Six randomized, double-blind trials (totaling several thousand participants driven mainly by the fluoxetine programs) evaluated three strategies: (i) dopaminergic/psychostimulant augmentation paired with structured therapy (levodopa; dextroamphetamine; methylphenidate and levodopa), and (ii) SSRI (fluoxetine 20 mg daily for 6 months) in routine rehabilitation [1–6].

Levodopa + physiotherapy (Scheidtmann et al., 2001)

In a prospective, randomized, double-blind trial (n=53), adults 3 weeks–6 months post-stroke received levodopa 100 mg (with carbidopa) or placebo 30 min before daily therapy for 3 weeks, then therapy alone for 3 weeks [1]. Rivermead Motor Assessment improved more with levodopa at 3 weeks (6.4 vs 4.1 points) and the advantage persisted at 6 weeks (8.2 vs 5.7; p=0.020) [1]. Tolerability was acceptable. This study highlights temporal coupling of dopaminergic facilitation with task-specific practice.

Dextroamphetamine + physiotherapy (STARS, 2006)

This multicenter, randomized, double-blind trial (n=71) started 5–10 days post-stroke and paired 10 mg dextroamphetamine or placebo with 10 therapy sessions over 5 weeks (twice weekly), targeting peak drug effect during training [2]. The primary Fugl-Meyer impairment scores improved in both groups; there was no overall between-group difference to 3 months [2]. An interaction in the moderate-severity subgroup favored drug, but this was confounded by baseline motor imbalance; thus, the authors concluded no proven benefit overall [2]. Safety was generally acceptable; one probable drug-related transient hallucination was reported.

Methylphenidate and levodopa + physiotherapy (Lökk et al., 2011)

In a 2×2 factorial, double-blind trial in chronic ischemic stroke, participants received methylphenidate (MPH), levodopa (LD), both, or placebo, each with standardized physiotherapy; assessments were at 15, 90 and 180 days [3]. All groups improved over time; at 6 months, small but statistically significant advantages over placebo were observed on Barthel Index and NIHSS, whereas motor superiority (eg, Fugl-Meyer) was not robust [3]. The regimen was well tolerated. Authors emphasized uncertainty about

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optimal dose, therapeutic window, and patient selection [3]. Synthesis of dopaminergic/psychostimulant trials. Collectively, these trials are biologically coherent and suggest potential for functional gains—especially when timed immediately before training (levodopa) [1,7]. However, sample sizes were modest, dosing/timing varied, and outcomes differed, limiting certainty for routine practice.

SSRIs (fluoxetine for 6 months)

FOCUS (2019)

In this pragmatic, multicenter, double-blind RCT (n=3,127), adults 2–15 days post-stroke received fluoxetine 20 mg or placebo daily for 6 months [4]. The primary outcome—shift in mRS at 6 months—was neutral (adjusted common OR =0.95; p=0.44) [4]. Fluoxetine reduced new depression but increased bone fractures, and other adverse events (hyponatremia, seizures) were more frequent [4,10].

AFFINITY (2020)

This double-blind RCT (n=1,280) replicated the design/dose in Australia/New Zealand/Vietnam and again found no improvement in mRS distribution at 6 months, with higher rates of seizure and hyponatremia and mania in the fluoxetine arm [5].

EFFECTS (2020)

In Sweden (n=1,500), fluoxetine did not improve mRS at 6 or 12 months and was associated with more infections, drowsiness, and hyponatremia at 6 months [6].

Synthesis of SSRI trials. Across three large, methodologically robust RCTs, fluoxetine for 6 months did not enhance global functional outcomes and was associated with more harms. The 2021 Cochrane review and a 2024 individual-patient-data meta-analysis of these trials confirmed no functional benefit and higher risks of fracture, falls with injury, seizures, and hyponatremia, despite fewer new depressions [10,14].

Table 1: Design snapshots of included RCTs

Trial (year)	Intervention (timing)	Rehab pairing	Phase post-stroke	Primary window	Main finding
Scheidtmann 2001 [1]	Levodopa 100 mg **30 min pre-PT** ×3 wks	Daily PT	3 wks–6 mo	3 & 6 wks	↑ Rivermead gains at 3 & 6 wks (p=0.020)
STARS 2006 [2]	Dextroamphetamine 10 mg with PT ×10 sessions/5 wks	PT twice weekly	5–10 days	6 wks–3 mo	No overall FM benefit; subgroup signal confounded
Lökk 2011 [3]	MPH, LD, both, or placebo (2×2)	Standardized PT	Chronic	15/90/180 days	Small BI/NIHSS advantages; motor not robust
FOCUS 2019 [4]	Fluoxetine 20 mg daily ×6 mo	Routine rehab	2–15 days	6 mo	Neutral mRS; ↑ fractures, other AEs; ↓ new depression

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AFFINITY 2020 [5]	Fluoxetine 20 mg daily ×6 mo	Routine rehab	2–15 days	6 mo	Neutral mRS; ↑ seizure/hyponatremia/ mania
EFFECTS 2020 [6]	Fluoxetine 20 mg daily ×6 mo	Routine rehab	2–15 days	6 & 12 mo	Neutral mRS; ↑ infections/drowsiness/ hyponatremia

Table 2: Selected outcomes and safety

Trial	Functional outcome (between-group)	Safety signals (fluoxetine trials and notable others)
Levodopa+PT 2001 [1]	Rivermead: +8.2 vs +5.7 at 6 wks (p=0.020)	Well, tolerated
STARS 2006 [2]	No overall FM difference	One transient hallucination; otherwise, acceptable
MPH/LD 2011 [3]	Small BI/NIHSS advantages at 6 mo	No notable side-effects reported
FOCUS 2019 [4]	Neutral mRS	↑ fractures, hyponatremia, seizures; ↓ new depression
AFFINITY 2020 [5]	Neutral mRS	↑ seizures, hyponatremia, mania
EFFECTS 2020 [6]	Neutral mRS	↑ infections, drowsiness, hyponatremia (6 mo)

DISCUSSION

This synthesis shows a split between dopaminergic/psychostimulant augmentation paired with therapy and SSRIs given for 6 months. Levodopa timed immediately before therapy improved motor outcomes in one well-designed trial [1], consistent with experience-dependent plasticity principles and reviews emphasizing that restorative drug effects depend on concurrent behavioral training [7]. By contrast, the three large fluoxetine trials—designed to detect global functional benefits—were consistently neutral and reported more harms, findings echoed by the updated Cochrane review and the 2024 individual-patient-data meta-analysis [4–6,10,14].

The STARS null result, with a confounded subgroup signal, illustrates how baseline imbalance, dose, and severity can shape apparent effects in small trials [2]. The methylphenidate/levodopa factorial trial suggests modest benefits on ADL and stroke severity at 6 months, but lacks robust motor superiority and leaves open questions about who benefits, how much, and when [3]. Together with mechanistic overviews, these data point to timing relative to therapy, phenotyping (severity/location), and dose as key levers for future research [7].

Guidelines remain clear: prioritize comprehensive, team-based, adequately dosed rehabilitation; consider pharmacologic enhancers selectively and within evidence-based frameworks [8,9]. Given the absence of functional benefit and the increased fractures, seizures, and hyponatremia with fluoxetine, do not prescribe SSRIs solely to “enhance recovery” after stroke; reserve them for psychiatric indications with risk–benefit monitoring [4–6,10,14]. For dopaminergic augmentation, especially levodopa immediately before

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therapy, the signal is promising but unproven at scale; use should be confined to research settings or carefully individualized cases with transparent outcome tracking [1,7–9,11,13].

Future trials should (i) align drug pharmacodynamics with therapy sessions; (ii) pre-specify phenotype-informed strata; (iii) select domain-specific outcomes sensitive to the hypothesized mechanism; and (iv) actively monitor safety (falls, fractures, seizures, hyponatremia) where relevant [7–10,14]. Adjacent evidence (DARS, BoTULS) informs symptom- or task-level targets (walking recovery; spasticity-related activities and pain), reinforcing the value of goal-directed, impairment-specific interventions within a comprehensive program [11,12].

CONCLUSION

In six randomized, double-blind trials specified, fluoxetine for 6 months did not improve global disability and increased adverse events, arguing against its routine use to enhance recovery. Levodopa timed before therapy improved short-term motor outcomes in one trial, and a small factorial study suggests modest ADL or stroke-severity advantages with methylphenidate/levodopa, but optimal dosing, timing, and phenotyping remain unresolved. Until high-quality confirmatory trials report, pharmacologic augmentation should be selective, mechanism-aligned, and embedded within comprehensive, team-based rehabilitation.

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